CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s024

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number	202293 S024
Priority or Standard	Priority
Submit Date	November 3, 2020
Received Date	November 3, 2020
PDUFA Goal Date	May 3, 2021
Divisions/Office	Division of Cardiology and Nephrology (DCN) & Division of Diabetes, Lipid Disorders, and Obesity (DDLO) / Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN), Office of New Drugs (OND)
Review Completion Date	April 30, 2021
Established/Proper Name	Dapagliflozin
Trade Name	Farxiga
Pharmacologic Class	Sodium-glucose co-transporter 2 (SGLT2) inhibitor
Applicant	AstraZeneca
Dosage form	Tablets
Applicant proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	709044004 |Chronic kidney disease (disorder)
Recommendation on Regulatory Action	Approve: • to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

	(b) (4)
Recommended Indication(s)/Population(s)	See above
Recommended SNOMED CT Indication Disease Term for each Indication	709044004 |Chronic kidney disease (disorder)
Recommended Dosing Regimen	10 mg once daily

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Glossary

ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
AKI	acute kidney injury
AR	adverse reaction
ARB	angiotensin receptor blocker
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CEA	Clinical event adjudication
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	cardiovascular
DMC	data monitoring committee
EC	executive committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
IND	Investigational New Drug
IP	investigational product
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PACD	primary analysis censoring date
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetic
PP	per protocol
PREA	Pediatric Research Equity Act

REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SED	study end date
UACR	Urine albumin-to-creatinine ratio

1 Executive Summary

1.1. Product Introduction

Dapagliflozin (trade name Farxiga) is an oral inhibitor of sodium glucose co-transporter 2 (SGLT2) that was approved on January 8, 2014 as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), on October 18, 2019 to reduce the risk of hospitalization for heart failure in patients with T2DM and established cardiovascular (CV) disease or multiple CV risk factors, and on May 5, 2020 to reduce the risk of CV death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

On November 3, 2020, AstraZeneca submitted an efficacy supplement for dapagliflozin for the following proposed indications:

(b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team agrees that the application provides substantial evidence of effectiveness that dapagliflozin reduces the risk of sustained eGFR decline, end-stage kidney disease (ESKD), CV death, and hospitalization for heart failure in adults with chronic kidney disease (CKD) at risk of progression.

(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

For Patients with Chronic Kidney Disease

(b) (4)

the Applicant conducted the DAPA-CKD trial, a randomized, double-blind, event-driven trial comparing dapagliflozin with placebo in 4,304 patients with an eGFR between ≥25 and ≤75 mL/min/1.73m^2 and urine albumin-to-creatinine ratio (UACR) ≥200 and ≤5000 mg/g on a maximally tolerated daily dose of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

DAPA-CKD met its primary endpoint, a composite of a ≥50% sustained decline in eGFR, ESKD (sustained eGFR <15 mL/min/1.73m^2, chronic dialysis, or receiving a kidney transplant), CV death, and renal death. After a median follow up of 28.5 months, 197 (9.2%) patients in the dapagliflozin arm and 312 (14.5%) patients in the in the placebo arm reached the primary endpoint (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.51, 0.72; 2-sided p<0.0001). The treatment effect was driven primarily by the renal components (sustained declines in eGFR and ESKD), although the CV death findings also favored dapagliflozin; there were few renal deaths. The absolute risk reduction was 2.9 events per 100 patient-years follow-up with a number needed to treat of 34 patients to prevent one primary endpoint event. The trial also met its first secondary endpoint, a composite endpoint that only included the renal components of the primary endpoint. The efficacy results were consistent in key subgroups, including across diverse etiologies of CKD. This suggests that dapagliflozin favorably impacts a common mechanism of CKD progression, although there is some uncertainty in subpopulations with few patients. It is also unclear whether these findings apply to populations the Applicant excluded from study because of concerns regarding effectiveness, specifically autosomal dominant and autosomal recessive polycystic kidney disease and patients with a recent history of immunosuppressive therapy for the treatment of kidney disease.

The trial also met other pre-specified secondary endpoints that assessed effects beyond kidney disease progression: fewer patients in the dapagliflozin arm experienced a hospitalization for heart failure or CV death event compared with patients on placebo (HR 0.71; 95% CI 0.55, 0.92; 2-sided p=0.009) and fewer patients in the dapagliflozin arm died of any cause compared with patients on placebo (HR: 0.69; 95% CI 0.53, 0.88; 2-sided p=0.0035). Although there was no pre-specified approach to testing the secondary endpoints after an unplanned interim analysis led to early termination of the trial, we believe the heart failure hospitalization findings are sufficiently robust based on both a low p-value and supportive data from outcomes trials in other populations that the results warrant an additional indication. The mortality findings appeared to be driven by effects on CV causes of death, for which the Applicant will get an indication based on other endpoints, but also non-CV causes of death, including infections and malignancies, via unclear mechanism. We believe it is reasonable to describe the results of this endpoint in the

clinical studies section of the label given the importance of this information to patients and providers; (b) (4)

While the DAPA-CKD trial enrolled a population with relatively advanced CKD at high risk of progression, data from the DECLARE trial provide supportive evidence of efficacy in a population with less advanced CKD. DECLARE was a multicenter, randomized, double-blind, placebo-controlled, event-driven, cardiovascular outcomes trial in patients with T2DM and preexisting CV disease or risk factors for CV disease. The trial was conducted to fulfill a post-marketing requirement issued at the time the drug was approved for glycemic control and was designed to exclude a 30% increase in the risk of major adverse cardiovascular events (MACE). The trial had two primary endpoints: MACE and a composite of hospitalization for heart failure and CV death. The trial also included a key secondary renal endpoint, a composite of a sustained ≥40% decrease in eGFR to an eGFR <60 mL/min/1.73 m^2, ESKD (dialysis ≥90 days, kidney transplant, or sustained eGFR <15 mL/min/1.73m^2), and renal or CV death. Although the secondary renal endpoint was to be tested within plans to control the overall type 1 error rate, the trial was not successful on the MACE endpoint. As such, there was no remaining alpha to test the secondary renal endpoint; however, fewer patients in the dapagliflozin arm experienced a renal composite endpoint event as compared with placebo (HR 0.76; 95% CI 0.67, 0.87; nominal p<0.001), an effect driven primarily by sustained declines in eGFR. DECLARE enrolled patients both with and without CKD at baseline, all with a creatinine clearance of >60 mL/min. Exploratory analyses limited to patients with evidence of CKD at baseline suggest that dapagliflozin is likely to delay the progression of CKD in patients with less advanced CKD than those enrolled in DAPA-CKD. (b) (4) these findings (b) (4) when viewed in the context of the DAPA-CKD results, we believe they provide support for granting a broader claim than would have been granted based on DAPA-CKD alone.

(b) (4)

Key Safety Findings in Patients with Chronic Kidney Disease
Potential risks of dapagliflozin in the DAPA-CKD trial, including in subgroups with and without diabetes and in patients with an eGFR <30 mL/min/1.73m^2, were largely consistent with those seen in previous trials of dapagliflozin in patients with T2DM and heart failure. There were fewer serious adverse events (SAEs) and adverse events with an outcome of death in the dapagliflozin group than in the placebo group. Overall, a similar proportion of patients in each group (5.5%) experienced an AE that led to study drug discontinuation, dose interruption, or dose reduction. AEs of volume depletion were reported in a slightly greater proportion of patients in the dapagliflozin arm compared with placebo (6% vs. 4%), but there was no difference in SAEs (0.7% in each group). There was no difference in amputation, diabetic ketoacidosis, fracture, or acute kidney injury events, all of which are AEs of interest for the SGLT2 inhibitor drug class.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CKD affects millions of people in the United States and leads to substantial morbidity and mortality. Approximately 1% of patients with CKD will progress to kidney failure and require either chronic dialysis or kidney transplant; risk factors such as albuminuria can help to identify patients at greater risk of progression. In addition, patients with CKD are at increased risk of cardiovascular events such as myocardial infarction, stroke, and heart failure.	CKD is common in the United States and is a serious disease associated with significant morbidity and mortality.
Current Treatment Options	• There are currently no approved therapies to delay the progression of kidney disease regardless of underlying etiology, although there are therapies approved for the treatment of specific causes of kidney disease (e.g., diabetic nephropathy in patients with T1DM or T2DM; autosomal dominant polycystic kidney disease). • Clinical management also involves risk factor modification, including glycemic control (for diabetic nephropathy), blood pressure control, lipid management, exercise, smoking cessation, and dietary modification.	There is unmet need for drugs to reduce morbidity and mortality in patients with CKD.
Benefit	*Patients with Chronic Kidney Disease* • Dapagliflozin was effective in slowing the loss of kidney function and delaying progression to ESKD and in reducing the risk of cardiovascular death in patients with CKD with reduced kidney	• The submitted data provide substantial evidence of dapagliflozin's effectiveness in reducing the risk of sustained eGFR decline, ESKD, CV death, and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	function (eGFR >25 to <75 mL/min/1.74m^2) and albuminuria (≥200 and ≤5000 mg/g) in the DAPA-CKD trial, a randomized, double-blind, event-driven trial comparing dapagliflozin 10 mg once daily with placebo. • Common etiologies of kidney disease in the trial included diabetic nephropathy (59%), ischemic/hypertensive nephropathy (16%), and IgA nephropathy (6%). The remaining patients spanned a wide range of other causes. Subgroup analyses suggest a benefit of dapagliflozin regardless of underlying etiology; however, the trial excluded patients with autosomal dominant and autosomal recessive polycystic kidney disease and patients with recent history of immunosuppressive therapy for the treatment of kidney disease because of concerns regarding effectiveness. • The DAPA-CKD trial enrolled a population with relatively advanced CKD at high risk of progression; however, exploratory analyses of data from the DECLARE trial, a randomized, double-blind, event-driven trial comparing dapagliflozin 10 mg once daily with placebo in patients with T2DM and CV disease or risk factors for CV disease, provided supportive evidence of a benefit of dapagliflozin on slowing the loss of kidney function in patients with T2DM and less advanced CKD. • Dapagliflozin also reduced the risk of hospitalization for heart failure or CV death (HR 0.71; 95% CI 0.55, 0.92; p=0.009) and death (HR: 0.69; 95% CI 0.53, 0.88; p=0.0035). (b) (4)	hospitalization for heart failure in adults with chronic kidney disease at risk of progression. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4)	
Risk and Risk Management	• Dapagliflozin 10 mg daily was well tolerated in the CKD population, including in subgroups with and without diabetes and patients with an eGFR <30 mL/min/1.73m^2. The safety profile in patients with CKD was consistent with the safety profile in other trial populations. • There were fewer SAEs and AEs with an outcome of death in the dapagliflozin group than in the placebo group. • Approximately 5.5% of patients in each group experienced an AE that led to study drug discontinuation, dose interruption, or dose reduction, most often for a renal-related event (< 1.5% in each group). • Volume depletion occurred more frequently with dapagliflozin than placebo (6% vs. 4%) but there was no difference in SAEs (0.7% in each group). • There was no difference in amputation, diabetic ketoacidosis, fracture, or acute kidney injury events.	Potential risks of dapagliflozin in patients with CKD were consistent with the findings in trials conducted for other indications. There was no difference in amputation, diabetic ketoacidosis, fracture, or acute kidney injury events, all AEs of interest for the SGLT2 inhibitor drug class.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☑	Patient reported outcome (PRO)	7.1.2 DAPA-CKD - Study Results
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Chronic kidney disease (CKD) is generally defined as abnormalities of kidney structure or function that are present for at least 3 months.[1] According to the Centers for Disease Control and Prevention, 31-34 million (14%-15%) people over 20 years of age in the U.S. meet criteria for CKD.[2] The most common underlying etiologies are diabetes and hypertension, although many other systemic diseases and primary kidney diseases lead to CKD. There are significant racial disparities in the development of CKD, with Black and Mexican American patients disproportionately represented compared with Whites.[3]

Progressive loss of kidney function leads to substantial morbidity, mortality, and disability,[4] including an increased risk of CV events such as myocardial infarction, stroke, and heart failure. By some estimates, approximately 1% of patients with CKD will progress to kidney failure requiring renal replacement therapy with either chronic dialysis or kidney transplant.[1]

2.2. Analysis of Current Treatment Options

There are currently no approved therapies indicated to delay the progression of kidney disease in the proposed broad population, although there are therapies approved for the treatment of specific causes of kidney disease.

There are currently four therapies indicated for the treatment of diabetic nephropathy in patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM) (Table 1). Captopril, an angiotensin converting enzyme inhibitor (ACEi) is indicated for the treatment of diabetic nephropathy in T1DM, while irbesartan and losartan, both angiotensin receptor blockers (ARBs), are indicated for the treatment of diabetic nephropathy in T2DM. In clinical practice, however, the kidney benefits of ACE inhibitors and ARBs are generally considered to be a class effect. In August 2020, a fourth agent, the SGLT2 inhibitor canagliflozin, was granted an indication to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria greater than 300 mg/day.

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[1] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.
[2] Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System—United States. website. http://www.cdc.gov/ckd
[3] Centers for Disease Control and Prevention. Age-adjusted prevalence of CKD Stages 1-4 by Race/Ethnicity 1999-2012. Chronic Kidney Disease (CKD) Surveillance Project website. https://nccd.cdc.gov
[4] Plantinga LC, Johansen K, Crews DC, et al. Association of CKD with disability in the United States. *Am J Kidney Dis.* 2011;57(2):212–227.

There are drugs approved for other specific causes of kidney disease as well, including diseases such as autosomal dominant polycystic kidney disease (ADPKD) and lupus nephritis.

In addition to approved therapies, clinical management to reduce the risk of kidney disease progression involves risk factor modification. This includes glycemic control (for diabetic patients), blood pressure control, lipid management, exercise, smoking cessation, and dietary modifications.

Table 1. Drugs Approved for the treatment of Diabetic Nephropathy

Product Name	Relevant Indication	Approval Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Angiotensin Converting Enzyme Inhibitors					
Captopril	Diabetic nephropathy (proteinuria >500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy	1994	25 mg three times a day	Captopril decreases the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for kidney transplantation or dialysis).	• Boxed warning for fetal toxicity • Anaphylactoid reactions • Head and neck angioedema • Intestinal angioedema • Anaphylactoid reactions during destination and membrane exposure • Neutropenia/agranulocytosis • Hepatic failure • Hypotension • Altered laboratory findings: hyperkalemia, hyponatremia, transient BUN/creatinine elevations, positive ANA • Cough
Angiotensin Receptor Blockers					
Irbesartan	Diabetic nephropathy in type 2 diabetes and hypertension, an elevated serum creatinine, and proteinuria (>300 mg/day)	2002	300 mg once daily	Irbesartan reduces the rate of progression of nephropathy (i.e., doubling of serum creatinine or end-stage renal disease [need for dialysis or kidney transplantation]) in a time-to-event analysis (HR: 0.80; 95% CI: 0.66 0.97; p=0.0234)	• Boxed warning for fetal toxicity • Impaired renal function • Hypotension in volume or salt-depleted patients • Hyperkalemia
Losartan	Diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2	2002	50mg once daily, increase to 100 mg once daily based on blood pressure	Losartan reduced the rate of progression of nephropathy (doubling of serum creatinine, end-stage renal disease (ESKD) [need for dialysis or transplantation), or death]) in a time-to -event analysis	• Boxed warning for fetal toxicity • Hypotension • Renal function deterioration • Hyperkalemia

Product Name	Relevant Indication	Approval Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
	diabetes and a history of hypertension.			(16.1% risk reduction; 95% CI:2.3% to 27.9%; p<0.022)	
Sodium-Glucose Transport Protein 2 Inhibitors					
Canagliflozin	to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day	2020	Dosing based on eGFR (mL/min/1.73m^2) - *eGFR≥60:* 100 mg once daily; dose may be increased to 300 mg daily - *eGFR 30-*≤60: 100 mg daily - *eGFR<30:* do not begin, however in patients with albuminuria>300 mg/day continue 100mg daily	Canagliflozin 100 mg significantly reduced the risk of end stage kidney disease (ESKD) (eGFR<15 mL/min/1.73 m^2), doubling of serum creatinine and cardiovascular death in a time-to-event analysis (HR: 0.70; 95% CI: 0.59, 0.82; p<0.01)	• Lower limb amputation • Volume depletion • Ketoacidosis • Urosepsis and pyelonephritis • Hypoglycemia • Necrotizing fasciitis of the perineum • Genital mycotic infections • Hypersensitivity reactions • Bone fractures

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dapagliflozin is marketed in the United States under the trade name Farxiga for three separate indications (Table 2). Dapagliflozin was initially approved in January 2014 during its second review cycle, as adjunct to diet and exercise to improve glycemic control in adults with T2DM. The initial application had initially received a Complete Response on January 17, 2012 because of marginal glycemic control and safety concerns, which were addressed by later trials.[5]

On October 18, 2019, dapagliflozin was approved to reduce the risk of hospitalization for heart failure in patients with T2DM and established cardiovascular disease (CVD) or multiple CV risk factors based on the results of the DECLARE study. (b) (4) .

Finally, on May 5, 2020, dapagliflozin was approved to reduce the risk of CV death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV) based on the results of the DAPA-HF trial.

Table 2 Indications and dosing regimens for dapagliflozin in the U.S.

Date	Indication	Dosing regimen
January 8, 2014	"as adjunct to diet and exercise to improve glycemic control in adults with diabetes mellitus"	5mg or 10 mg orally once daily
October 18, 2019	"to reduce the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus and established CVD or multiple CV risk factors"	10 mg orally once daily
May 5, 2020	"to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV)"	10 mg orally once daily

Source: Clinical Reviewer

There are three dapagliflozin-containing fixed-dose combination products marketed in the United States, all approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM. Xigduo XR is a dapagliflozin and metformin combination product approved on October 29, 2014; Qtern is a dapagliflozin and saxagliptin combination product approved on

[5] Safety concerns with the initial application included hepatotoxicity, CV safety, and bladder cancer risk. All of these safety concerns were addressed with the DECLARE trial.

February 27, 2017; and Qternmet XR is a dapagliflozin, saxagliptin and metformin extended-release combination product approved On May 2, 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

The presubmission/regulatory activity discussed in this section is focused on activity pertinent to the proposed new indications.

Over the course of dapagliflozin's development program, there were multiple interactions with the Agency. Table 3 shows key milestones, agreements, and advice provided to the Applicant. For a summary of pediatric pre-submission regulatory activity, refer to Section 9.

Table 3. Summary of key presubmission regulatory activity

Source	Agency advice
27-Jul-2016 FDA pre-IND Meeting FDA link	*Primary efficacy endpoint* FDA advised that a single trial (DAPA-CKD) with a composite endpoint driven by the occurrence of ≥ (b) (4)% sustained decline in eGFR and a (b) (4) may not be adequate for an dication; however, in this case, it may be possible to rely on supportive evidence from other trials in the dapagliflozin program (i.e., DECLARE). *Population* FDA noted that most enrolled subjects are likely to have diabetic nephropathy and/or hypertensive nephrosclerosis and that ultimately, the nature of the indication would depend on the population enrolled and may be limited to a subpopulation if the results suggest the benefit is limited to that subpopulation. FDA recommended that the sponsor carefully characterize CKD etiology. The Division concurred with the sponsor's plan to require that at least 30% of subjects have T2DM and at least 30% not have diabetes. *Dose selection* (b) (4) The Applicant indicated they planned to study 10 mg (b) (4) *Background medications* The FDA agreed that subjects with diabetic nephropathy should be on stable, maximum tolerated doses of an ACE inhibitor or ARB. The Division reiterated that it was important that the care of concomitant medical conditions that may impact study endpoints achieve contemporary U.S. treatment goals in both treatment arms. *Statistical analysis* The FDA advised that the statistical analysis plan should specify a plan for testing the secondary endpoints within a plan to control the overall type 1 error rate. In addition, the FDA did not recommend the that the trial be stopped at an interim analysis unless there was a benefit on CV mortality or progression to ESKD. The rationale for this advice was to ensure that the data for the benefit-risk analysis would be robust enough to support approval of the proposed indication and subgroup analyses.

	Because the populations in DECLARE (CrCl≥ 60 mL/min/1.73 m^2) differed from DAPA-CKD (eGFR <75 mL/min/1.73 m^2), and use of ACE inhibitor/ARB was not specified in DECLARE, FDA did not recommend the trials be combined in a meta-analysis. *Safety* FDA agreed that the size and duration of exposure in DAPA-CKD was likely adequate for the proposed indication.
15-Nov-2016	DAPA-CKD IND submission (IND 130647)
23-Aug-2019 Fast Track FDA link	FDA granted Fast Track designation for the following proposed indication: FARXIGA® is indicated to delay the progression of renal failure and prevent cardiovascular and renal death in patients with chronic kidney disease.
18-Oct-2019 Approval of Dapagliflozin for new indication	Dapagliflozin 10 mg was granted an indication to reduce the risk of hospitalization of heart failure in patients with T2DM and established CVD or multiple CV risk factors. (b) (4)
18-Dec-2019 Advice Letter FDA link	The FDA issued an Advice Letter detailing concerns regarding the collection of renal endpoint data in the DECLARE study (NDA 202293 S-018); refer to Section 7.1.4 for detailed discussion.
30-March-2020	AstraZeneca notified the FDA that the DAPA-CKD trial would be stopped early for overwhelming efficacy on the recommendation of the trial's Data Monitoring Committee (DMC).
3-April-2020 Breakthrough Therapy Designation Advice teleconference FDA link	During a scheduled teleconference to obtain advice from the Agency regarding Breakthrough Therapy Designation, the Agency and Applicant discussed the Applicant's decision to terminate the DAPA-CKD trial early for overwhelming efficacy and events leading to the decision, as documented in the internal meeting minutes and discussed in relevant sections of this review. The Applicant noted that the DMC spoke with firewalled members of the trial's Executive Committee on March 27, 2020, and they agreed that the trial should be terminated due to overwhelming efficacy. The Applicant stated that the study team had previously decided to forgo a planned formal interim analysis independent of the DMC deliberations, in part because of anticipated difficulties with closing out the trial early because of COVID-19. The Applicant did not know if the DMC was aware of this decision or whether that impacted the DMC deliberations. The Division asked whether the DMC reviewed results of the primary and key secondary endpoints outside of a formal interim analysis. The applicant noted that the DMC charter allowed for the DMC to ask for analyses they would like to see, but the Applicant was unaware what analyses were requested or reviewed to inform the decision.
16-Apr-2020 Type C meeting for DAPA-CKD and DECLARE	*Indication* FDA agreed that, in principle, the DECLARE renal endpoint data, in addition to a positive DAPA-CKD trial, could support an efficacy supplement (b) (4) The wording of the indication and the nature of the claim would be a

FDA link	review issue. *Safety* The FDA agreed to the Applicant's proposal to not pool DAPA-CKD and DECLARE safety data.
10-Aug-2020 FDA meeting (minutes 25- Sept-2020) FDA link	The Applicant provided an overview of the design and results of DAPA-CKD trial.
30-Sept-2020	Breakthrough Therapy Designation was granted

Source: Clinical Reviewer compiled information from the submission package

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

The following sections have been deleted from the review, as there was no relevant information submitted in the supplement for these sections: Clinical Microbiology, Devices and Companion Diagnostic Issues, and Nonclinical Pharmacology/Toxicology.

4.1. Office of Scientific Investigations (OSI)

Although the application met mission critical criteria implemented during the COVID-19 pandemic, [6] clinical site inspections were not conducted as part of the review of this application because there were no site-specific safety or efficacy concerns to warrant inspections. In addition, few investigators had significant financial disclosures and the disclosures were not expected to impact conclusions regarding efficacy or safety (see Section 12.2). Discussions with Suyoung Tina Chang from the Office of Scientific Investigations confirmed that there were no site-specific concerns that would warrant inspections.

4.2. Product Quality

Pallaiah Thammana from the Office of Pharmaceutical Quality reviewed the Environmental

[6] Mission critical criteria included: public health emergency (includes COVID-19 response activities), life Saving/Life Extending (ex. PEPFAR), new Molecular/Chemical Entity (including in a food animal), rare diseases and orphan products, opioid studies, studies associated with determining the impact of products associated with human and/or animal food safety (i.e. residue depletion studies), complaints or allegations of Human Subject Protection (HSP) concerns with imminent harm, serious Data Integrity Concerns affecting Safety/Efficacy – imminent health hazard to humans or animals, drug shortage, first Generic/Competitive Generic (CGT), and products with Medical Countermeasures (MCM) Designation.

Assessments submitted by the Applicant. The review will be filed separately.

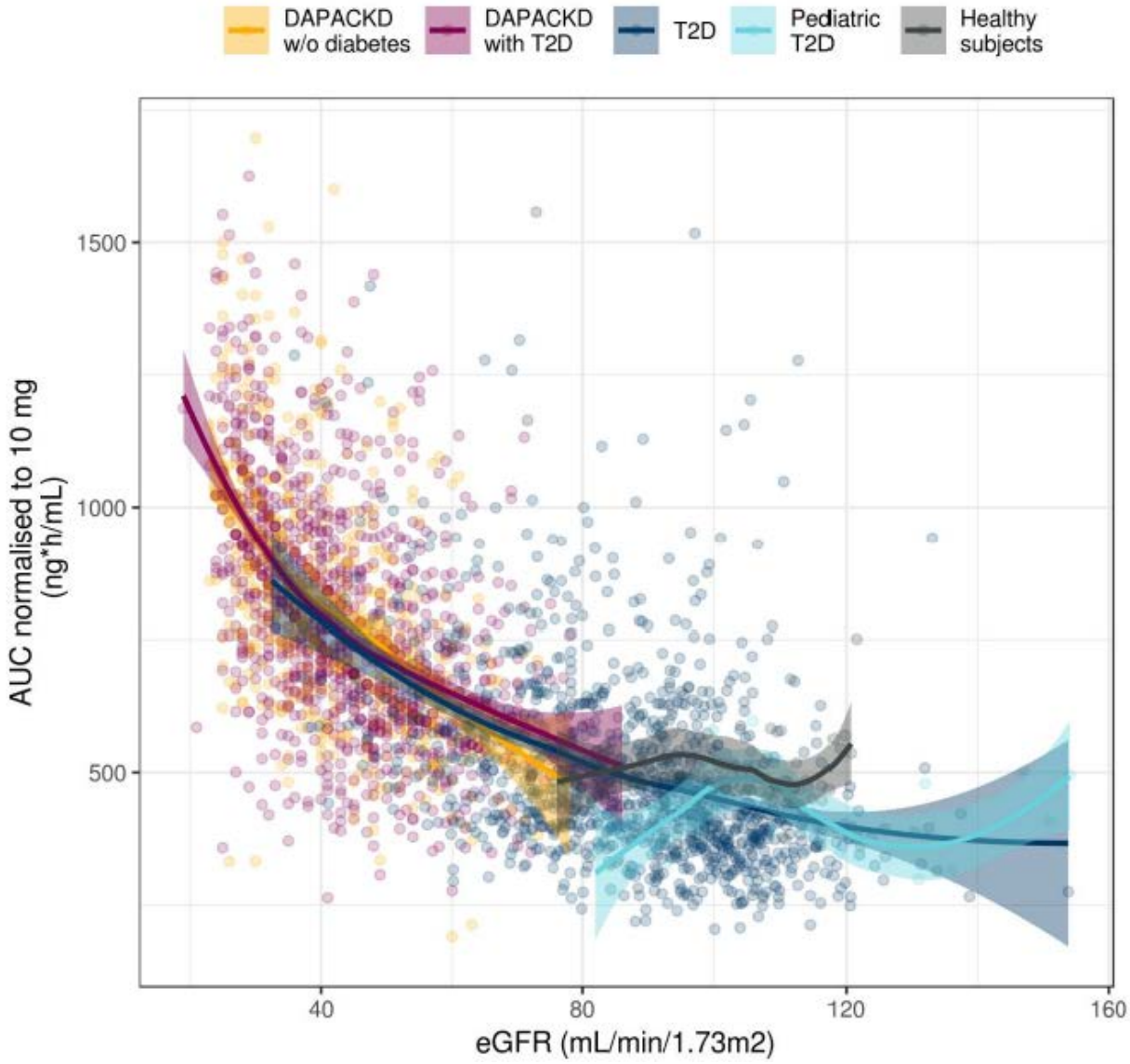
5 Clinical Pharmacology

In this submission, the Applicant provided an updated population pharmacokinetic (PK) analysis that incorporated PK data from patients with CKD into their previously developed dapagliflozin population PK model. (b) (4) The main clinical pharmacology attributes of dapagliflozin in adult and pediatric patients with T2DM were reviewed previously by Ritesh Jain (reviews filed February 17, 2013, February 4, 2015, and February 16, 2016).

The recommendation from the Office of Clinical Pharmacology is to accept the proposed 10 mg dapagliflozin dose for patients with CKD.

The key question for this clinical pharmacology review is:
Is an alternative dosing regimen or management strategy required for patients with renal impairment?
No, the PK of dapagliflozin 10 mg in CKD patients confirm the previous findings in the T2DM population and are not increased beyond the range of observed exposures in the T2DM development program. Dapagliflozin pharmacokinetics were not found to differ between patients with CKD, T2DM, or both conditions. Figure 5-1 illustrates the relationship between dapagliflozin exposure (AUC) corrected for dose and eGFR for five evaluated populations included in the updated population PK model. The central tendency of this relationship overlaps between each population. Further, while the CKD population has lower mean eGFR values and thus higher dapagliflozin AUC, the model estimated AUC values do not greatly exceed the range of values observed in the T2DM or T2DM population with CKD. The pharmacokinetics of dapagliflozin and the covariate relationship of eGFR on dapagliflozin clearance are reasonably described by the updated population PK model. See Appendix 12.3, Pharmacometrics Review for further details.

Figure 5-1. Dapagliflozin AUC Normalized to 10 mg versus eGFR, Stratified by Population. Lines represent the loess smooth for the respective population. Circles indicate population PK predicted AUC values.



Source: Applicant's Population PK Report, Figure 10

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

There are two clinical studies pertinent to the current submission, DECLARE and DAPA-CKD.

DECLARE was previously reviewed by the FDA.[49] DECLARE was an event-driven, randomized, double-blind, placebo-controlled, cardiovascular outcomes study evaluating the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM with CV risk factors or pre-existing CV disease. DECLARE was conducted to fulfill a post-marketing safety requirement issued at the time of approval of the indication for glycemic control. No additional efficacy data were included in the current submission.

DAPA-CKD was an event-driven, randomized, double blind, placebo-controlled study evaluating the effect of dapagliflozin 10 mg once daily in patients with CKD with and without T2DM. The objective was to evaluate the effect of dapagliflozin on the progression of CKD and renal and CV death.

The current submission includes study data for DAPA-CKD and references the previous submission of DECLARE; the main characteristics of these studies are shown in Table 4.

Table 4. Listing of clinical studies relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized	Study Population
Controlled Studies to Support Efficacy and Safety						
DECLARE D1693C00001	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Dapagliflozin 10 mg once daily Matching placebo 1 tablet once daily Oral administration	**Primary endpoints:** • Composite of cardiovascular death, myocardial infarction, or ischemic stroke (MACE)[d] • Composite of hospitalization for heart failure or CV death. **Secondary endpoints:** • Composite of sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2, ESKD (dialysis ≥90 days or kidney transplantation, sustained eGFR <15 mL/min/1.73m^2), and renal or CV death • All-cause mortality	Median of 50.2 months (4.2 years)[a]	17,160	Adults ≥ 40 years of age with T2DM and either (1) established CV disease, or (2) multiple CV risk factors[c]
DAPA-CKD D169AC00001	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Dapagliflozin 10 mg once daily Matching placebo 1 tablet once daily Oral administration	**Primary endpoint:** time-to-first event of composite of ≥ 50% sustained decline in eGFR, ESKD, CV or renal death **Secondary endpoints:** • Composite of ≥50% sustained decline in eGFR, ESKD, or renal death • Composite of CV death or hospitalization for heart failure • All-cause mortality	28.5 months (2.4 years) median time[b]	4,304	Adult ≥ 18 years of age with CKD defined as (1) eGFR ≥25 and ≤75 mL/min/1.73 m^2 (CKD-EPI formula), and (2) UACR ≥200 and ≤5000 mg/g. The study included patients with and without T2DM.

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio.
[a] Time from randomization to date of completion/withdrawal from study or death
[b] Time from randomization until the earliest of death, withdrawal of consent, or last visit
[c] Multiple CV risk factors defined as ≥ 55 years of age for men, ≥ 60 for women, and at least one of the following: dyslipidemia, hypertension, or current tobacco use

6.2. Review Strategy

This was a joint multi-disciplinary review. Tania Condarco and William Koh reviewed the data from DAPA-CKD supporting efficacy and the relevant efficacy portions of the previously submitted DECLARE data (NDA 202293 S-018). Tzu-Yun McDowell reviewed the safety data for DAPA-CKD.

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. DAPA-CKD: A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease, (study code: D169AC00001)

Trial Design

"A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease," referred to as DAPA-CKD (NCT03036150) in this review, was an international, multicenter, event-driven, randomized, double-blind, placebo-controlled study. The study objective was to investigate the effect of dapagliflozin 10 mg relative to placebo as an adjunct to standard-of-care (stable and maximum-tolerated dose of an ACEi or ARB) in patients with and without diabetes with established CKD (eGFR ≥25 and ≤75 mL/min/1.73 m^2) and albuminuria (UACR ≥200 and ≤5000 mg/g).

Patients were randomized at 385 sites in 21 countries. The study was expected to continue until 681 primary endpoint events had accrued for an anticipated duration of 45 months, although the protocol specified that the study could be terminated early if the Data Monitoring Committee (DMC) determined that dapagliflozin was associated with either a clear benefit or harm.

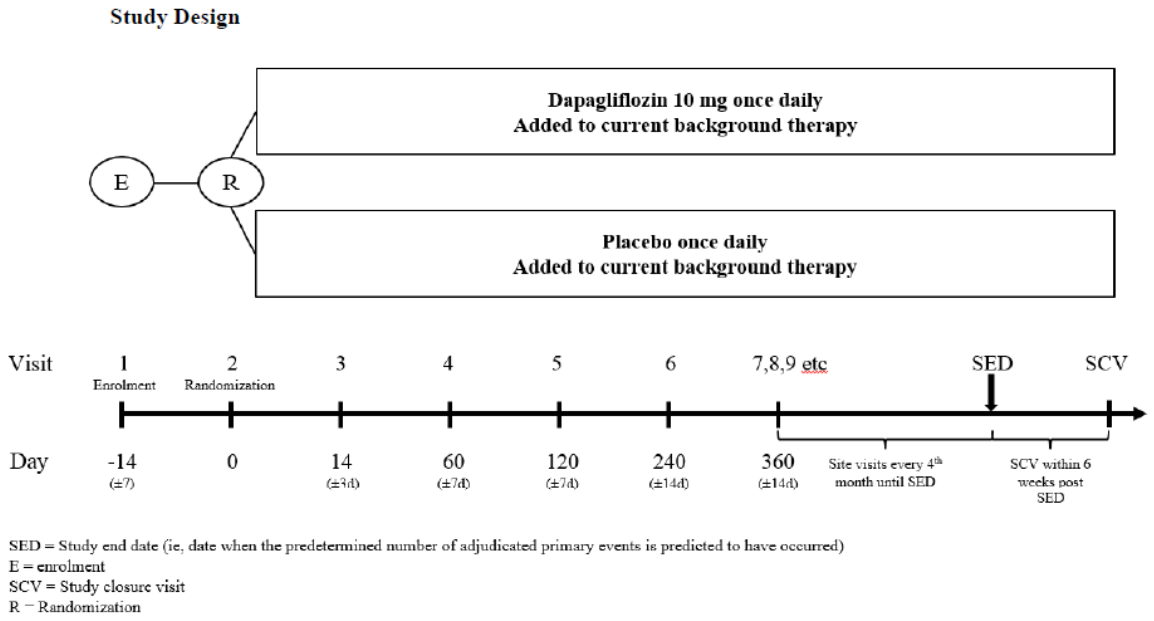
During the enrollment period (visit 1), eligibility criteria and central laboratories were assessed to determine eligibility.[7] Eligible patients were randomized at visit 2. Study visits occurred at 2 weeks, 2, 4, and 8 months, and every 4 months thereafter. Both eGFR and UACR were collected at each study visit.[8] Study Closure Visits (SCVs) were to be conducted within 6 weeks of the

[7] In addition to central laboratories, because it was expected that failure to meet eGFR/albuminuria criteria would result in the majority of screen failures, the protocol specified an optional local laboratory assessment of eGFR and/or albuminuria for pre-screening of patients expected to meet all other entry criteria.
[8] If patients did not agree to continue study visits according to plan, they could have modified follow-up with adjustments to subsequent visits (i.e., less frequent visits, regular phone contacts, a contact at study closure, or other means).

global study end date (SED). A schematic of the trial design is shown in Figure 2

Reviewer's comment: The more frequent visits early in the trial were consistent with FDA advice. In July 2016, FDA recommended an early assessment of kidney function after drug initiation due to decreases in eGFR previously seen as early as 1 week after initiation of dapagliflozin.

Figure 2 DAPA-CKD Study Design



SED = Study end date (ie, date when the predetermined number of adjudicated primary events is predicted to have occurred)
E = enrolment
SCV = Study closure visit
R – Randomization

Source: CSR, Figure 1

The study was designed to enroll a broad population of patients with impaired kidney function and albuminuria. To ensure an approximate balance between treatment groups, randomization was stratified by patients with and without T2DM (requiring a minimum of 30% in each sub-population) and UACR (>1000 mg/g; ≤1000 mg/g). The number of patients with an eGFR of 60 to 75mL/min/1.73m^2 at the time of randomization (based on the value at visit 1) was capped to not exceed ~10%.

Reviewer's comment: During the July 2016 pre-IND meeting, the FDA agreed with the Applicant's plan to require that at least 30% of patients have T2DM and that at least 30% of patients not have T2DM. Review of the Applicant's communications with investigators showed that patients with T2DM and those with an eGFR >60 mL/min/1.73 m^2 were enrolled faster; therefore, investigators were encouraged at times to focus enrollment on patients without T2DM and with an eGFR <60 mL/min/1.73 m^2.

Key Inclusion Criteria:

- eGFR ≥25 and ≤75 mL/min/1.73m^2 (CKD-EPI formula) at visit 1
- UACR ≥200 and ≤5000 mg/g at visit 1

  Version 2 of the protocol also required evidence of increased albuminuria ≥3 months before visit 1
- Use of stable (for at least 4 weeks before visit 1) and maximally tolerated daily dose of ACEi or ARB, if not medically contraindicated

Key Exclusion Criteria:

- Autosomal dominant or autosomal recessive polycystic kidney disease, lupus Nephritis, or ANCA-associated vasculitis
- Receiving cytotoxic therapy, immunosuppressive therapy, or another immunotherapy for primary or secondary renal disease within 6 months prior to enrolment
- History of organ transplantation
- Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrollment or previous intolerance of an SGLT2 inhibitor
- T1DM
- New York Heart Association (NYHA) class IV heart failure at the time of enrolment
- Myocardial infarction, unstable angina, stroke or transient ischemic attack within 12 weeks prior to enrolment
- Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 weeks prior to enrollment is planned to undergo any of these procedures after randomization

Reviewer's comment: The eligibility criteria allowed for the enrollment of a broad population of patients with kidney disease compared with similar trials that have focused on a more homogenous population (e.g., diabetic kidney disease).

Investigational Drug Dosing:

Patients received visually identical tablets of either dapagliflozin 10 mg or placebo. Study drug was taken orally at approximately the same time each morning. If clinically indicated, 5 mg of dapagliflozin/placebo could be used (further discussion below); however, the dose was to be increased to 10 mg as soon as clinically indicated.

Reviewer's comment: (b) (4) *Based on these comments, the Applicant chose to study only the 10 mg dose.* (b) (4)

(b) (4)

Concomitant Medications:
The protocol specified detailed collection of CKD[9] and CV medications throughout the study, including any time endpoint events or adverse events were recorded.

Patients were to be treated according to regional standards of care for CV risk factors (i.e., blood pressure, lipids, and antithrombotic agents), diabetes,[10] and CKD complications (i.e., hyperphosphatemia, hyperparathyroidism, hyperkalemia, acidosis, and anemia). As noted above, ACEi or ARB use was required per the trial's eligibility criteria.

The DMC monitored treatment goals (i.e., blood pressure and HbA1c) and concomitant medications to ensure that standard of care was being followed. If goals were not met, the DMC was to report the need for additional measures to the Executive Committee.

To avoid confounding of efficacy results and for safety reasons, the use of off-label SGLT2 inhibitors was specifically prohibited.

Reviewer's comment: The importance of standard of care treatments and goals was emphasized in the DMC charter and in communications with investigators. Although the use of SGLT2 inhibitors in patients with CKD was not considered standard of care during the time that DAPA-CKD was being conducted, the Applicant was concerned that updates to the American Diabetes Association 2019 Standards of Care[11] based on the CREDENCE trial would increase the use of open label SGLT2 inhibitors; therefore, the Applicant emphasized that off-label SGLT2 inhibitors were not to be used during the trial.

Discontinuation of Investigational Product, Withdrawals, and Premature Trial Termination:
Patients were free to discontinue study drug at any time but were to continue scheduled follow-up according to the study protocol until study closure.

Permanent discontinuation of study drug was permitted for the following reasons:
- Patient's decision
- Adverse event or other safety reason, per the investigator's opinion
- Severe non-compliance with protocol
- Confirmed diabetic ketoacidosis (DKA); temporary interruption if suspected DKA

[9] CKD medications included: RAAS inhibitors: ACEI/ARB, renin inhibitors, mineralocorticoid antagonists; diuretics: loop diuretics, thiazides, other diuretics; cytotoxic agents, immunosuppressive agents, or other immunotherapy; other: phosphate binders, potassium binders.
[10] Patients with T2DM at randomization were to continue their T2DM treatment. For applicable patients, a reduction of insulin by 10-20% of the total daily dose or a reduction of sulfonylurea dose by 25-50% was recommended for patients with an HbA1c ≤7% at randomization.
[11] American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019 [web annotation]. Diabetes Care 2019;42(Suppl. 1):S103–S123.

- Positive pregnancy test

A temporary decrease in dose to 5 mg was recommended for either unexpected acute declines in eGFR or volume depletion/hypotension. In both cases, patients were to be evaluated and medical problems addressed and contributing concomitant medications decreased/stopped, if needed, before changes were made to study drug dosing.

The protocol stipulated that disease modifying agents (i.e., ACEi/ARBs for patients with proteinuric CKD and ACEi/ARBs, sacubitril/valsartan, mineralocorticoid receptor antagonists, and beta blockers for patients with heart failure) should not be reduced in dose or discontinued unless all other measures failed to improve the clinical situation.

Temporary interruption of study drug was recommended for patients with an acute medical illness resulting in volume depletion or for patients undergoing surgery. The protocol encouraged investigators to restart randomized study drug and to maintain a dose of 10 mg once the patient's condition was stable.

Patients could withdraw informed consent for study participation at any time. Investigators were to collect as much data as possible (especially vital status) at study closure even for patients who withdrew consent, as allowed by local privacy laws.

Trial termination was at the discretion of the Applicant and also depended on the DMC recommendations.

Reviewer's comment: The protocol did not require discontinuation of study drug after a patient initiated dialysis. In fact, the National Lead Investigator (NLI) committee's Frequently Asked Questions document[12] encouraged investigators to continue study drug during dialysis treatment. A total of 29 patients in the dapagliflozin arm and 47 patients in the placebo arm had at least one day of respective exposure after starting dialysis; see exposure information for these patients in Appendix 12.5.

Treatment Compliance

Treatment compliance was assessed by the amount of study drug dispensed and the amount of study drug returned by the patient (i.e., pill counts).

Study Administrative Structure and Committees

The following committees had oversight over the trial:

- *Executive Committee (EC):* The EC was comprised of international leading scientists and non-voting members of AstraZeneca and operated under an EC charter. The EC was responsible for the study design, protocol amendments, and statistical analysis plan;

[12] National Lead Investigator committee slides dated November 3, 2017 and February 27, 2018

supervising study conduct and progress; interpretation of the final results; and making recommendations to the Applicant regarding early stopping or modifications of the study based on information received from the DMC.

- *National Lead Investigator (NLI) Committee:* The NLI Committee was comprised of national leaders from each country where the study was conducted. The NLI committee was supervised by the EC and was responsible for providing clinical guidance on study implementation, recruitment, and study conduct in their respective country.
- *Data Monitoring Committee (DMC)*: An independent DMC comprised of clinical and statistical experts monitored the trial to ensure patient safety. The DMC operated under a DMC charter.[13] The DMC reviewed unblinded study data[14] at regular intervals. The DMC recommended to the EC whether the study should be either discontinued, modified, or continue.
- *Clinical Event Adjudication Committee (CEA):* The CEA was comprised of a CEA chair , co-chair, a nephrology scientific co-chair, and CEA physician reviewers. The role of the CEA was to independently review and interpret potential endpoint events. For each applicable event, two physician reviewers conducted blinded adjudication, as per the CEA charter. Refer to Figure 21. for a summary of how events were identified and adjudicated.
- *Diabetic Ketoacidosis Adjudication Committee (DKA-AC):* The DKA-AC provided independent, blinded adjudication of potential cases of DKA by expert endocrinologists as per a DKA Adjudication Manual.

The Applicant provided minutes and slides for meetings of the EC, NLI, CEA, and DMC. Relevant information regarding these communications is included throughout the review.

Identification and Adjudication of Events of Interest

Events of interest were captured via four venues: first, via the investigator, who questioned patients and reviewed medical records; second, via the central laboratory, which notified investigators of any of the following: serum creatinine values >2 times recent value, eGFR<15 mL/min/1.73m^2, or ≥50% decline in eGFR and requested retest after 4 weeks and preferably no later than 6 weeks; third, via the Applicant who reviewed source documentation and eCRF data; and fourth, via CEA review during adjudication of another event.

Events were adjudicated as outlined in the CEA charter; refer to Table 45 in the appendix for detailed definitions of events of interest. The pre-specified definitions used for adjudication were generally in agreement with previous FDA discussions and/or conformed with published

[13] The same DMC monitored both the DAPA-CKD and DAPA-HF studies. The first DMC review occurred when approximately 200 randomized patients had at least one SAE; subsequent reviews occurred every 4-6 months.
[14] A Statistical Data Analysis Center was responsible for providing the DMC with analyses for review, conducting the planned interim analysis (which was not done for DAPA-CKD), preparing summary notes of the closed and open sessions, and storing notes for the closed sessions.

standardized definitions.[15] The following events were submitted for central blinded adjudication:

- All deaths: classified as CV,[16] non-CV, and renal death (death due to ESKD when dialysis was not administered)
- Renal events:
    - Dialysis
    - Kidney transplantation
    - Acute kidney injury (defined as a doubling of serum creatinine compared to most recent central laboratory measurement)[17]
- CV events:
    - Hospitalization for heart failure
    - Cardiac ischemia events (myocardial inflation and unstable angina)
    - Cerebrovascular events (stroke and transient ischemic attack)

The following were recorded in the eCRF but *not* adjudicated: eGFR decline of ≥50% (from baseline and from most recent central laboratory measurement), eGFR<15 mL/min/1.73m^2,[18] and new diagnosis of T2DM.[19]

Study Endpoints

Primary Endpoint:
Time to the first occurrence of any of the components of the composite:

- ≥50% sustained (based on two consecutive central laboratory values at least 28 days apart)[20] decline in eGFR
- Reaching ESKD, defined as:
    - sustained eGFR <15 mL/min/1.73m^2 (based on two consecutive central laboratory values at least 28 days apart)[20] or
    - chronic dialysis (dialysis ongoing for at least 28 days or when ESKD is deemed

[15] Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation.* 2015;132:302–361.
[16] For the purposes of the primary and secondary endpoints, the SAP included deaths adjudicated as "undetermined deaths" in the analysis of CV deaths.
[17] This was a safety endpoint that could be positively adjudicated repeatedly in any given patient during the study.
[18] eGFR events detected by a local laboratory were to be confirmed by a central laboratory. The central laboratory would notify the investigator if eGFR was <15mL/min/1.73m^2 or there was ≥50% decline in eGFR from baseline and request a re-sampling after 4 weeks and preferably no later than 6 weeks after the first sampling.
[19] Defined as initiation of anti-diabetic medication or HbA1c ≥6.5% measured by central laboratory at two consecutive study visits.
[20] The start date of the event was the date of the first of the two qualifying consecutive central laboratory values. The retest was preferably not to be done later than 6 weeks after the first sample. A retest was not required if the specific eGFR endpoint was already confirmed for a patient.

    - irreversible and dialysis was stopped before day 28) or
    - receiving a kidney transplant
- CV death[21]
- Renal death

Reviewer's comment: The primary endpoint reflects discussions with the FDA at the July 2016 pre-IND meeting and is consistent with the FDA's advice. Although the FDA agreed with the components of the proposed primary endpoint, it suggested that sustained eGFR <15 mL/min/1.73m^2 not be classified as an ESKD event to be consistent with the CDISC definition for Diabetic Kidney Disease (December 2016). The Applicant, however, believed the definition was consistent with other contemporaneous trials and therefore chose to maintain eGFR <15 mL/min/1.73m^2 as part of the ESKD definition.

In addition, as per FDA advice, version 2 of the protocol removed the requirement for adjudicating potential eGFR-based endpoints because these events could be identified based on objective laboratory data.

Review of the EC meeting minutes show that the EC discussed the importance of collecting adequate data for potential chronic dialysis events. The EC chairs sent letters directly to investigators reminding them to report "as much information as possible in case a patient needs dialysis."

Secondary Endpoints:
There were three secondary endpoints, which were to be tested in the following hierarchical sequence:

1. A composite of a sustained ≥50% decline in eGFR, ESKD, or renal death (identical to the primary endpoint but without CV death)
2. Time to the first occurrence of the components of the composite:
    - CV death[21]
    - Hospitalization for heart failure
3. Time to death of any cause

Exploratory endpoints
The protocol included several exploratory endpoints, (b) (4)

- Changes in UACR from baseline
- Time to the first occurrence of each of the following central laboratory potassium values: >6 mmol/L, >5.5 mmol/L, <3.5 mmol/L, and <3 mmol/L
- Time to the first occurrence of an event of doubling of serum creatinine (compared to the most recent central laboratory measurement)

[21] Deaths adjudicated as 'cause undetermined' were included in endpoint analyses as CV deaths.

Reviewer's comment: The exploratory endpoints are not adequate to support labeling claims, and, as such, these endpoints will not be discussed further in this review.

In addition, there were two exploratory endpoints that assessed patient-reported outcomes (see Section 7.2.5):

- Change from baseline in the overall summary score of KDQOL 36[22]
- Change in health status as measured by EQ-5D-5L

Statistical Analysis Plan

Amendments

The initial SAP (Version 1) was dated February 1, 2017 and was revised once, on April 15, 2020 (version 2), after protocol version 4.0 was finalized and the Applicant had announced early termination of the study and study closeout. In version 2, the SAP was revised to align the SAP with previous amendments to the protocol.

The following were changes pertinent to key efficacy assessments: clarification that eGFR-based endpoints would not be adjudicated (in accordance with protocol amendment 2), inclusion of exploratory MACE and renal endpoints (in accordance with protocol amendment 3), clarification that doubling of serum creatinine would be analyzed as time-to-first event (in accordance with protocol amendment 3), and removal of a planned formal interim analysis and associated updates to the alpha level for the final analysis (in accordance with protocol amendment 4). The revised SAP also clarified that eGFR analyses would be based on central laboratory serum creatinine values, provided additional details regarding subgroup analyses,[23] and defined baseline in relation to the date of randomization.

In general, there were no changes to the statistical analysis methods or changes to the hierarchy of endpoints in the multiplicity testing strategy that could have been driven by potential knowledge of unblinded study results.

Datasets

The full analysis set (FAS) consisted of all patients randomized. Patients were analyzed according to their randomized assignment regardless of whether they discontinued study treatment. Unless otherwise specified, all efficacy analyses were based on the FAS.

The safety analysis set was based on all patients who received at least one dose of randomized

[22] The KDQOL 36 is an abbreviated form of the KDQOL, which combines generic and disease-specific components for assessing the health-related quality of life of patients with CKD. Scores range from 0 to 100, with higher scores reflecting better quality of life.

[23] Added Japan and UK to regional subgroups, removed ACEi/ARB use as a subgroup variable due to small sample size of patients not on an ACEi/ARB, clarified two variables for subgroup analysis (T2DM at baseline and UACR at baseline), and clarified that subgroup analysis would be conducted for all secondary endpoints.

treatment. Patients were analyzed based on the actual treatment received. If patients received both treatments, then the treatment assignment was based on the randomized assignment.

Statistical Conventions

Study data until the SED were included in the primary and secondary efficacy endpoint analyses. April 3, 2020 was considered the SED, also known as the primary analysis censoring date (PACD).

In the SAP, a month was defined as 30 days; therefore, a patient-year was defined as 360 days for this study.

Descriptive statistics were used to summarize key baseline demographics, disease characteristics, and use of concomitant medications and were based on the FAS. Continuous variables were summarized using the minimum, 25th percentile, mean, median, 75th percentile, maximum, and standard deviation. Binary or categorical variables were summarized as counts and percentages.

Baseline eGFR and UACR were defined as the arithmetic means of the values from visits 1 and 2. If a patient was rescreened, the arithmetic mean of the latest values for visits 1 and 2 was used. If only one value was available, that was used as baseline. The eGFR values were calculated based on central laboratory serum creatinine values using the CKD-EPI equation. Baseline for other variables was defined as the last value on or prior to the date of randomization.

Reviewer's comment: The definition of baseline eGFR was consistent with the July 2016 FDA advice. In order to account for variability in eGFR, FDA recommended that the average of multiple measurements be used for baseline.

Interim Analysis

Protocol versions 1.0 through 3.0 and SAP version 1.0 specified that an interim analysis, based on the Haybittle-Peto rule, was planned when 75% of adjudicated primary events had accrued. At the interim analysis, superiority of dapagliflozin compared to placebo for the primary efficacy endpoint was to be declared if the interim one-sided p-value was <0.001. If the study was stopped for superiority, testing of the secondary endpoints was to be based on a one-sided p-value of 0.001. This planned interim analysis was removed with protocol version 4.0 and SAP version 2.0. See the section below on Data Quality and Integrity for additional discussion.

Control of Overall Type 1 Error Rate

Based on SAP version 2.0, a closed testing procedure was used to control the family-wise type 1 error at a one-sided level of 0.025 (or equivalently, a two-sided level of 0.05). The procedure first evaluated the primary composite endpoint then proceeded down the pre-specified hierarchy for the key secondary endpoints, if the preceding endpoint was rejected at a one-sided 0.025 level. The procedure was to stop if the null hypothesis for the preceding endpoint

was not rejected at a one-sided 0.025 level.

The trial was stopped after the DMC conducted an unplanned interim efficacy analyses, which the applicant acknowledged could lead to inflation of the overall type 1 error. Further, there was no pre-specified approach to testing the secondary endpoints after an unplanned interim analysis. The Applicant proposed a post-hoc, retrospective approach to control the family-wise type 1 error rate based on Glimm et al. 2010,[24] considering the degree of correlation between the primary and secondary endpoints. In absence of pre-specification, the statistical reviewer noted that the approach was difficult to interpret.

Analysis of Primary and Secondary Endpoints

The primary composite endpoint was analyzed as the time from randomization to the first event. Patients without an endpoint event were censored at the earliest date of withdrawal of informed consent, non-CV death, or non-renal death where applicable, and otherwise at the earliest date of last clinical event assessment or the PACD. The number and percent of patients with an event and event rates were presented by arm. Event rates were calculated as the ratio of the number of patients with an event divided by the total duration of follow-up by treatment arm.

A Cox proportional hazards (PH) regression was used to analyze the primary efficacy endpoint, adjusting for treatment group and baseline eGFR as a continuous variable, and stratified by randomization factors (a combination of T2DM status and UACR). Efron's method was used to break ties. The estimated hazard ratio (HR), Wald-based 95% confidence interval (CI), and p-values based on the Score statistic were reported from the regression model. In addition, Kaplan-Meier estimates of the cumulative incidence were reported. In this review, the statistical reviewer reported Wald-based p-values for consistency with the 95% CI.

The secondary endpoints and each component of the primary and secondary composite endpoints (regardless of the occurrence of other components) were analyzed as time-to-first event in a manner similar to the primary composite endpoint. The individual components included:

- ≥50% sustained decline in eGFR
- ESKD
- Sustained eGFR <15 mL/min/1.72m^2
- Chronic dialysis
- Kidney transplant
- Renal death
- CV death
- Hospitalization for heart failure

[24] Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2010;29(2):219-28.

According to the Analysis Data Reviewer's Guide, the following hierarchy of importance was used to determine the contributing component for the endpoint in the event of ties:

1) Sustained eGFR <15 mL/min/1.72m^2
2) Sustained ≥50% decline from baseline in eGFR
3) Chronic dialysis
4) Kidney transplant
5) Death

Subgroup Analyses

Subgroup analyses were prespecified for the following baseline characteristics:

- Age: (≤65, > 65 years)
- Sex: (male, female)
- Race: (White, Black or African American, Asian, Other)
- Geographic region: (Europe, Asia, North America, Latin/South America)
- Baseline Type 2 diabetes status: (Yes, No)
- Baseline UACR category: (≤1000, >1000)
- Baseline eGFR: (< 45, ≥45; < 30, ≥30 mL/min/1.73m^2)
- Baseline systolic BP: (≤130; >130 mmHg)

The statistical reviewer also conducted subgroup analyses by etiology of CKD (diabetic nephropathy, ischemic/hypertensive nephropathy, chronic glomerulonephritis, other or unknown cause of CKD) because these subgroups were considered important from a clinical perspective. Further, the statistical reviewer conducted a subgroup analyses in patients with "chronic glomerulonephritis" that restricted the analysis to those with a biopsy-confirmed diagnosis.

Subgroup analyses of both primary and key secondary efficacy endpoints used the same Cox PH model fitted within each level of the subgroup. In addition, interactions were evaluating using a Cox PH model that included subgroup and treatment and subgroup variables. The estimated HR and respective 95% CI were reported within each subgroup category provided at least 15 events occurred in total.

The SAP specified the following exploratory endpoints:

- Sustained eGFR decline from baseline of ≥30% and ≥40%
- Composite of chronic dialysis, kidney transplant and renal death
- Myocardial infarction
- Stroke
- First occurrences of serum potassium falling above/below defined thresholds
- Doubling of serum-creatinine

The SAP specified that the change in eGFR from baseline was fit using a two-slope mixed effects linear spline model with Day 14 as the knot. The model adjusted for treatment group,

stratification factors and baseline continuous eGFR, continuous time, and time by treatment interaction. The model included random effects for the intercept, acute slope, and chronic slope. An unstructured variance covariance matrix is used to model within patient errors. For this analysis, only on-treatment eGFR measurements were included. Linear contrasts, respective difference in least square (LS) means comparing dapagliflozin with placebo, and respective 95% CI were specified to estimate the acute (from baseline to Day 14), chronic (Day 14 through Month 30), and total slope (from baseline through Month 30) in eGFR. The total slope was specified to be evaluated at 30 months since randomization.

The exploratory endpoints, changes from baseline over time for eGFR, UACR, HbA1c, body weight, SBP, KDQOL-36, and EQ-5D-5L were each fit to a mixed model repeated measures (MMRM) regression model adjusting for treatment group, visit, visit by treatment interaction, and continuous baseline. These analyses included on-treatment measurements only. Analysis of HbA1c only included patients with T2DM at baseline. UACR measurements were log transformed before analysis. The estimated differences for dapagliflozin compared to placebo, respective 95% CIs, and two-sided p-values were reported. In addition, the eGFR and UACR data were presented graphically based on the MMRM model described previously. Adjusted LS means at specific visit weeks were graphed over time.

For the proportions of patients with a new diagnosis of T2DM, the binary response was fit using a logistic regression adjusting for treatment group and baseline continuous HbA1c.

For the proportion of patients with CKD Stage 4 during study, the binary response was fit using logistic regression adjusting for treatment group and baseline eGFR. For these two binary endpoints, the odds ratios, respective 95% Wald-based CIs, and two-sided Wald-based p-values were reported.

The time-to-first incidence of doubling of serum creatinine was not reviewed further because the SAP specified that the first doubling was relative to the most recent assessment and not relative to baseline, which is more likely to reflect acute injury than efficacy in delaying chronic progression of underlying kidney disease.

Sample Size Calculations

Sample size was calculated based on accrual of 681 primary endpoint events. This estimate provided a statistical power of 90% to demonstrate superiority of dapagliflozin over placebo with a HR of 0.78[25] at a one-sided alpha of 2.5%. Assuming an annual event rate of 7.5%[26] in the placebo group, 4,000 patients were estimated to provide an adequate number of primary events over a 24-month recruitment period and expected 33-month follow-up period.

[25] The assumed hazard ratio was derived from the kidney findings in the EMPA-REG trial of empagliflozin in patients with T2DM.
[26] This event rate was based on review of the published literature in the CKD population.

Handling of Missing Data and Sensitivity Analyses

Patients who had incomplete follow-up or were prematurely censored due to withdrawal of consent or loss-to-follow-up were considered to have missing information for the primary efficacy analysis.

The SAP specified sensitivity analyses to assess the impact of missing follow-up data, including a tipping point analysis; however, the SAP did not provide adequate detail to reproduce the analyses. Based on the description provided in the Analysis Data Reviewer's Guide, the Applicant imputed primary efficacy outcomes for patients who were censored before the PACD, regardless of the reason for incomplete follow-up (except death). The steps were as follows:

1. The hazard rate for the placebo arm was estimated based on all follow-up since randomization in the placebo group, adjusting for baseline stratification factors. For the dapagliflozin arm, this hazard rate was multiplied by the estimated hazard ratio.
2. A new event time was simulated using the hazard rate estimated in 1. The patient would be considered an event if this simulated event occurred earlier than the difference in the time between the date of censoring to a minimum of the date of PACD and date of death. If this event time was earlier, the censored patient would be imputed as an event with this event time added to the current follow-up.
3. Step 2 was repeated 1000 times for each of the patients with missing observed follow-up. This generated 1000 imputed datasets.
4. Then the same Cox PH model used in the primary analysis was applied to each of the datasets.
5. Rubin's rule was used to combine the 1000 hazard ratios and 95% CIs.

To address the impact of missing follow-up for these patients, the Applicant conducted the tipping point analysis by repeating the imputations in Step 2 and systematically shifting the dapagliflozin hazard rates until the results was no longer statistically significant, while holding the placebo hazard rate fixed.

The Applicant used observed information (# of events / total patient follow-up) from all randomized patients to estimate the hazard rates by treatment arm and imputed the missing follow-up time (i.e., time from the last clinical assessment to the PACD) for patients who were censored before the PACD; however, this approach is based on a missing at random assumption and assumes the hazard rates for patients with missing eGFR assessments would be the same as the hazard rates estimated from the patients in the study with complete eGFR assessment regardless of adherence to treatment; therefore, the statistical reviewer requested an additional analysis that imputes the missing follow-up time since the last eGFR assessment based on patients who discontinued randomized treatment but remained in the study through the PACD. For this approach, the two-piece exponential hazard rate with a cut-point of 240 days was used.

In addition, the Applicant conducted the following multiple imputation analysis by accounting for a patient's on- and off-treatment status:

- The on-treatment hazard rate was used to impute missing follow-up for on-treatment missing follow-up.
- The off-treatment event rate was used to impute off-treatment missing follow-up events.

Patients who did not have complete eGFR assessments were imputed based on the hazard rate according to their on- and off-treatment status.

The statistical reviewer conducted a simple tipping point analysis using the Applicant's additional analysis as a starting point. For each treatment arm, a multiplicative factor ($\delta_{Reference}$, $\delta_{Dapagliflozin}$) ranging from 0.2 to 5 was applied to both the on- and off-treatment hazard rate. A factor less than 1 indicates that the number of events imputed is less frequent than the reference hazard rates while a factor greater than 1 indicates that the number of events imputed is more frequent. Then, multiple imputations were conducted for each combination of δ's to impute the events, producing 1000 imputed datasets. A Cox PH model was used to analyze each dataset and Rubin's rule was used to combine the results. The statistical reviewer acknowledged that, ideally, the tipping point would be four-dimensional, (i.e., allow deltas for the on- and off-treatment hazard rates) to more comprehensively describe the space. However, this approach allows a simple description of the tipping point space.

Protocol Amendments

The original protocol (version 1) was approved on October 26, 2016. In total, there were four versions of the global protocol with additional changes to local protocols;[27] refer to Table 43 in the appendix for a summary of global protocol changes in relation to other trial conduct documents. A summary of the global protocol amendments is shown in Table 5.

[27] Argentina's local protocol specified additional pregnancy testing. Canada's local protocol changes included additional exclusion criteria (active bladder cancer, history of DKA within a month of visit 1, history of ≥2 major hypoglycemia events within 1 month prior to enrollment) and additional information regarding necrotizing fasciitis of the perineum and its reporting. China's local protocol noted that in addition to above, if eGFR decreased more than 30% from randomization at Visit 3 (after approximately 2 weeks of treatment), a dose reduction of study drug to 5 mg should be considered and an unscheduled visit was recommended. If eGFR decreased more than 50% from randomization at the unscheduled visit, or at Visit 3, an interruption of study drug was recommended and the patient's condition re-evaluated. Restarting or increasing the dose later was encouraged. Germany's local protocol specified that all AEs were to be recorded in the eCRF. India's local protocol specified that all components of the primary and secondary efficacy endpoints fulfilling SAE criteria in Indian sites were to be reported to the Indian health authorities per local regulatory requirements in a blinded manner. Japan's local protocol also added exclusion criteria based on prescribing information and added an extra visit on Day 28. Sweden's local amendment specified the storage place for samples until disposed. The United Kingdom's local protocol clarified that "history" of elevated urinary protein results or elevated albuminuria could be used in in the inclusion criteria, since in clinical practice urine protein (rather than albuminuria) is measured. The U.S. local protocol amendment included text specifying when it may be acceptable to temporarily interrupt concomitant treatment (e.g an ACEi/ARB if the patient experienced a significant deterioration in kidney function; a beta-blocker if the patient is unduly bradycardic or hypotensive; a, MRA if the patient has hyperkalemia, etc.).

Table 5 Protocol amendments

Protocol Version	Changes
Version 1 October 26, 2016	Original version of the protocol created.
Version 2 September 26, 2017	*Safety*: Expanding AEs of interest to amputations; additional information regarding evaluation of volume status and investigational product dose reduction/interruption; clarification of AEs of interest (for renal events); limiting the AEs recorded to exclude laboratory results only (for renal events) unless fulfilling serious adverse event (SAE) criteria or discontinuation criteria; limiting AEs reported to health authorities to heart failure and fatal AEs; clarifying standard of care treatment after patient stops study drug; adding guidance regarding treatment of acute worsening heart failure and other acute conditions. *Prohibited medications:* clarification that open label SGLT2i in combination with study drug is not permitted. *Endpoint:* Removing the requirement to adjudicate potential endpoint events related to eGFR decline. *Recording of concomitant medications:* CV medications are to be recorded in detail in the eCRF during the study *Interim analysis:* Clarifying that the DMC could do more than one interim analysis of efficacy, if necessary.
Version 3 January 22, 2020	*Exploratory endpoints added:* (1) to determine if dapagliflozin vs. placebo will result in a reduction in the incidence of the composite of chronic dialysis, renal death, or receiving a kidney transplant, (2) to determine if dapagliflozin vs. placebo will result in a reduction in the incidence of the composite endpoint of CV death, MI, or stroke.
Version 4 March 17, 2020	*Interim analysis:* removal of information pertaining to the interim analysis[28] since it was foreseen that the outcome of this analysis would be close to the study end date. Due to the removal of the interim analysis, the statistical testing level for endpoints was corrected to 2.5% instead of 2.496%.

Abbreviations: AEs: adverse events, SAEs: serious adverse events, SGLT2i: sodium glucose co-transporter 2 inhibitor, eGFR: estimated glomerular filtration rate; CV: cardiovascular; DMC: Data monitoring committee; MI: myocardial infarction.
Source: Clinical Reviewer

Reviewer's comment: Changes to the global protocol were generally consistent with advice provided by the FDA.

7.1.2. DAPA-CKD - Study Results

Financial Disclosure

The Applicant adequately disclosed financial interests; the financial disclosure findings are unlikely to affect the overall trial results (refer to Section 12.2 for details).

Blinding

Individual treatment codes could be broken at the investigator's discretion in cases of medical emergencies and when management of the patient required this knowledge. In total, there were 121 (2.8%) patients who were unblinded (59 [2.7%] and 62 [2.9%] patients randomized to dapagliflozin and placebo, respectively).

Data Quality and Integrity

General Considerations
Data were submitted by the Applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed under the network path \\CDSESUB1\evsprod\NDA202293.

In general, the quality of the submitted datasets was acceptable, and datasets were carefully documented. The relevant flags used for the primary and secondary efficacy analyses were described sufficiently in the Analysis Data Reviewer's Guide. The statistical reviewer was able to verify that the baseline data used to stratify patients for randomization was submitted in the SDTM dataset and to reproduce the primary and key secondary analyses without noticeable deviations.

Potential Concerns Related to the Unplanned Interim Analysis and Removal of Planned Analysis
Given that the trial was terminated early based on an unplanned efficacy analysis, we reviewed the steps taken by the Applicant, EC, and DMC leading to the decision and study closeout, including the EC meeting minutes and presentations, the DMC closed and open session minutes, reports, and presentations, and other relevant documentation.[29]

Review of the DMC meeting materials revealed that the DMC monitored accumulating efficacy endpoint events during the trial, including event numbers, 95% CIs, and Kaplan-Meier plots. The DMC noted in the October 29, 2019 closed meeting session that the "95% confidence intervals for both the CEA-confirmed and unrefuted primary outcome incidence rate do not overlap between treatment groups, suggesting a strong treatment effect." Given these findings and the published results of the CREDENCE and DAPA-HF studies, the DMC asked the Statistics Collaborative to perform a "an inferential efficacy analysis" for the March 26, 2020 DMC meeting. In a March 10, 2021 response to an FDA information request, the Applicant confirmed that the circumstances leading to this inferential look were considered unplanned from a

[29] The October 29, 2019 and March 26, 2020 DMC recommendation forms were electronically signed on July 22, 2020. In an information request dated January 28, 2020, the Applicant clarified that the Statistics Collaborative had requested that the forms be re-signed electronically. The Applicant provided the original forms that were manually signed on the dates of the meetings.

design perspective and that the analysis was "triggered primarily by the exceptional strength of the accumulating data." The analysis was ultimately based on 408 events (60% of the 681 planned events).

During the review cycle, the Applicant provided additional information regarding the protocol amendment removing the preplanned formal interim efficacy analysis that was to occur after accrual of 75% of primary endpoint events (681 events). The review team noted that the amendment was issued nearly simultaneously with the unplanned interim analysis, and the rationale for the amendment was not clear from the EC meeting minutes and slides (see Table 44 in the appendix). According to the minutes, the EC had discussed changing or removing the interim analysis but decided against doing so because it would necessitate a "substantial amendment," which would be a lengthy process.[30] They also noted that earlier stopping may lead to less robust data in non-diabetic patients.[31] In response to an information request, the Applicant provided minutes and slides from a February 28, 2020, regularly scheduled meeting of the Development Review Committee, an AstraZeneca internal governance body. The minutes documented the decision to remove the formal interim analysis based on the anticipated impact of the COVID-19 pandemic on data quality and the short timeline between the planned interim analysis and the projected trial completion date. Based on that meeting, on March 3, 2020, the AstraZeneca DAPA-CKD project team informed the EC chairs of the Development Review Committee recommendation during an operational meeting, and, on March 11, 2020, the EC informed the DMC of the decision.

We note that this unplanned interim analysis did not include the following provisions, which would generally be pre-specified for a planned interim analysis: a monitoring rule to allow for an earlier interim analysis, a plan for alpha spending for testing the key secondary endpoints, and a plan if the DMC decided not to stop the study. We note, however, that the primary efficacy endpoint was overwhelmingly significant at a $p<0.0001$, and the Haybittle-Peto boundary specified for the pre-planned interim analysis (i.e., one-sided $p<0.001$) was very conservative such that, even with the interim analysis at an earlier timepoint, the results were strong enough to allow early stopping without significant concern that inflation of the overall type 1 error rate could impact interpretation of the trial's findings. Based on our review of the trial documents and the Applicant's responses to our information requests, it also does not appear that changes to the interim analysis were informed by knowledge of accruing trial data. As such, we do not have concerns regarding trial integrity or interpretation of the trial's findings.

Patient Disposition

In total, 7,517 patients were enrolled in the study, of which 3,213 patients were not randomized. Most non-randomized patients were ineligible due to not meeting albuminuria or

[30] See EC minutes dated September 3, 2019 and November 9, 2019
[31] Per the October 29, 2019 open session DMC meeting minutes

eGFR inclusion criteria.[32] A total of 4,304 patients were randomized equally to dapagliflozin or placebo. The median time in the study (until the study end date) was 27.6 months.

Over 99% of patients continued in the study (i.e., were not lost to follow-up and did not withdraw consent for follow-up) (Table 6). Vital status at the end of the study, either through public records or last study contact, was known for all but five patients. The proportion of patients who discontinued randomized treatment was similar across arms. The most common reason for discontinuation of study drug was subject decision, followed by discontinuation due to adverse events; refer to the safety section for further discussion of the latter.

Table 6 Patient disposition

	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)	All (N=4304)
Continued Study [1]	2142 (99.5%)	2147 (99.8%)	4289 (99.7%)
Alive at Final Study Contact	2036 (95%)	1988 (92%)	4024 (93%)
Dead at Last Contact	106 (5%)	159 (7%)	265 (6%)
Discontinued Study	10 (<1%)	5 (<1%)	15 (<1%)
Lost to Follow-Up [2]	2 (<1%)	2 (<1%)	4 (<1%)
Withdrawal of Consent [3]	8 (<1%)	3 (<1%)	11 (<1%)
Discontinued Randomized Treatment	274 (13%)	309 (14%)	583 (14%)
Subject decision	142 (6%)	160 (7%)	302 (7%)
Adverse event	118 (5%)	123 (6%)	241 (6%)
Other [4]	13 (<1%)	20 (<1%)	33 (<1%)
Severe non-compliance	1 (<1%)	3 (<1%)	4 (<1%)
Discontinuation criteria [5]	0	3 (<1%)	3 (<1%)

1: Defined as patients who were not lost to follow-up and did not withdraw consent for follow-up; Date of last ascertainment for completed study in this table is July 3, 2020.
2: Patients did not have known vital status by July 3, 2020.
3: As of July 3, 2020, seven dapagliflozin and two placebo patients were alive; one dapagliflozin patient and two placebo patients had died; vital status was unknown for one placebo patient.
4: Most common "other" reason for discontinuation was "investigator's decision." Four (0.2%) dapagliflozin and six (0.3%) placebo patients discontinued study drug due to worsening kidney disease (either worsening kidney function, starting dialysis, or kidney transplant). One patient in each treatment arm discontinued study drug after starting an open label SGLT2 inhibitor.
5: Protocol specified discontinuation criteria that led to study drug discontinuation: confirmed DKA (one patient) and positive pregnancy test (two patients)
Source: Statistical Reviewer

[32] 1,856 (57.8% or enrolled patients) did not meet the albuminuria criteria of evidence of increased albuminuria 3 months or more before visit 1 and UACR ≥200 and ≤5000 mg/g at visit 1
1,331 (41.4% of enrolled patients) did not met the eGFR criteria: eGFR ≥25 and ≤75 mL/min/1.73m^2 (CKD-EPI Formula) at visit 1.

A total of 81% of randomized patients completed follow-up, defined as having a primary efficacy endpoint event, being censored at the PACD, or being dead by the PACD. A total of 19% of randomized patients were censored before the PACD because of incomplete eGFR assessments (Table 7).

Table 7 Characterization of Follow-up of Primary Endpoint through PACD, DAPA-CKD

	Dapagliflozin (N=2152)	Placebo (N=2152)	All (N=4304)
Completed Follow-up [1]	1730 (80%)	1742 (81%)	3472 (81%)
Had Primary Endpoint Event	197 (9%)	312 (14%)	509 (12%)
Censored at PACD	1504 (70%)	1388 (64%)	2892 (67%)
Dead	29 (1%)	42 (2%)	71 (2%)
Did not Complete Follow-up	422 (20%)	410 (19%)	832 (19%)
Withdrawal of Consent [2]	7 (<1%)	3 (<1%)	10 (<1%)
Missing eGFR assessments	415 (19%)	407 (19%)	822 (19%)
Total missing patient-years excluding death [3]	285.7	267.3	553

1: Patients who had a primary efficacy endpoint, were censored at PACD, or were dead before PACD were considered to have completed follow-up.
2: Based on PACD date of April 3, 2020
Abbreviations: PACD=primary analysis censoring date; eGFR=estimated glomerular filtration rate
Source: Statistical reviewer

Protocol Violations/Deviations

Important protocol deviations[33] are shown in Table 8. Important protocol deviations occurred in approximately 2.6% of patients and were balanced between treatment arms. The most common protocol deviation was failing to meet the inclusion criteria of stable ACEi or ARB for 4 weeks prior to study start, seen in 1.1% of the population. A total of 14 patients (0.3% of the randomized population) used open-label SGLT2 inhibitors during the study.

[33] Important protocol deviations were defined as meeting any of the following : patients who were randomized but did not meet inclusion and exclusion criteria; patients who received the wrong study treatment at any time during the study; and patients who received a prohibited concomitant medication.

Table 8 Important protocol deviations-FAS

Protocol Deviation Coded Term; N (%)	Dapagliflozin 10mg (N=2152)	Placebo (N=2152)	All (N=4304)
Patients with at least 1 important deviation	61 (2.8)	52 (2.4)	113 (2.6)
Randomized patients who did not fulfill all inclusion criteria	52 (2.4)	46 (2.1)	98 (2.3)
Stable treatment with ACEi or ARB for at least 4 weeks before visit 1, if not medically contraindicated	23 (1.1)	24 (1.1)	47 (1.1)
Signed informed consent prior to any study specific procedures	5 (0.2)	7 (0.3)	12 (0.3)
Cytotoxic therapy, immunosuppressive therapy or other immunotherapy for renal disease within 6 months prior enrolment	4 (0.2)	5 (0.2)	9 (0.2)
eGFR >=25 and <=75 ml/min/1.73 m^2 at enrolment (visit 1)	4 (0.2)	5 (0.2)	9 (0.2)
Known blood-borne diseases.	4 (0.2)	3 (0.1)	7 (0.2)
Participation in another clinical study with an IP during the last month prior to enrolment	4 (0.2)	2 (0.1)	6 (0.1)
Hepatic impairment (AST or ALT >3x ULN or total bilirubin >2x ULN at time of enrolment).	3 (0.1)	0 (0)	3 (0.1)
Increased albuminuria 3 months before visit 1 and UACR >=200 and <=5000 mg/g at visit 1	2 (0.1)	1 (<0.1)	3 (0.1)
MI, unstable angina, stroke or TIA within 12 weeks prior to enrolment	2 (0.1)	0 (0)	2 (0.1)
Any important PD not applicable to the predefined categories	1 (<0.1)	0 (0)	1 (<0.1)
Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis	1 (<0.1)	0 (0)	1 (<0.1)
PCI, CABG or valvular repair/replacement within 12 weeks prior to enrolment or planned after randomization	1 (<0.1)	0 (0)	1 (<0.1)
SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor	0 (0)	1 (<0.1)	1 (<0.1)
Women of child-bearing potential who are not willing to use a medically accepted method of contraception, OR have a positive pregnancy test OR are breast-feeding	0 (0)	1 (<0.1)	1 (<0.1)
Patient took incorrect investigational treatment i.e. IP not allocated through IWRS	1 (<0.1)	0 (0)	1 (<0.1)
Patient received prohibited medications during IP period i.e. SGLT2 Inhibitor	8 (0.4)	6 (0.3)	14 (0.3)

Abbreviations: FAS=full analysis set; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; eGFR=estimator glomerular filtration rate; AST=aspartate transaminase; ALT=alanine transaminase; ULN=upper limit of normal; UACR=urinary albumin-to-creatinine ratio; MI=myocardial infarction; TIA=transient ischemic attack; PD=protocol deviation; ANCA=anti-neutrophil cytoplasmic antibody; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; SGLT-2=sodium glucose co-transporter 2; IWRS=interactive web response system; IP=investigational product
Source: Clinical reviewer generated from ADDV.xpt dataset and CSR table 14.1.2

Reviewer's comments: Overall there were few and similarly distributed important protocol deviations. It is not likely that these protocol deviations would bias the efficacy findings.

COVID-19 Impacts

The end of the study coincided with the global COVID-19 pandemic.[34] To minimize disruptions to study conduct, the Applicant implemented additional measures to ensure adequate monitoring and collection of laboratory samples. No COVID-19-related protocol violations were considered important per the definition above.

Sites performed on-site and remote SCVs.[35] Despite the pandemic, 99.8% of all SCVs were completed.[36] In March 2020, the Applicant developed a home delivery service to provide study drug for patients who could not come to the study site. Unlike on-site SCV visits, however, remote SCV visits did not allow for laboratory data collection (reported as a protocol deviation).[37]

The unexpected early termination of the trial (based on a DMC recommendation) concurrent with the pandemic resulted in a delay in the shipping of laboratory kits to study sites for SCVs.[38] Shipping restrictions also limited the shipping of samples to central laboratories, and investigators were provided guidance on storage of samples if shipment was not possible. Shipping of study drug from patients to sites (to assess compliance) was also compromised; therefore, this information was captured verbally from patients.

Reviewer's comment: Because most primary efficacy data was collected in the period preceding the pandemic and pandemic-related challenges impacted both treatment arms, it is unlikely that the pandemic biased the overall trial results.

Demographic Characteristics

Baseline characteristics were generally well balanced (Table 9). A total of 33% of the randomized patients were female, and the average age was 62 years. Most patients were White (53%) followed by Asian (34%); Blacks made up 4% of the randomized population. The most common geographic region for enrollment was Asia (31%) followed by Europe (29%); a total of 12% of patients enrolled in the United States.

[34] COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020.
[35] The eCRFs could be completed in person or as part of a telephone visit; therefore, travel restrictions had limited impact on study visits. Since the trial was completing, the Applicant did not revise the eCRF modules to collect COVID-19-related data. Information related to the impacts of COVID-19 was collected via protocol deviations to the extent feasible.
[36] 73% were completed as on-site visits, and 27% were completed as remote visits.
[37] Even for in-person SCV visits, some tests were cancelled, not collected, or the results not recorded due to COVID-19 related reasons (i.e., prolonged time of shipment to central laboratory, not all sites had SCV kits)
[38] If the SCV laboratory kit was not available, sites were asked to use unscheduled visit kits or premature treatment discontinuation visit kits because the content was the same.

The mean baseline eGFR was 43 mL/min/1.73m^2 (Table 9), and median UACR was 950 mg/g (see Figure 23 in the appendix for a scatter plot of the baseline eGFR by the baseline UACR).

Table 9 Demographic and Baseline characteristics

	Dapagliflozin 10 mg (N=2152)	**Placebo (N=2152)**	**All (N=4304)**
Female	709 (33%)	716 (33%)	1425 (33%)
Age[1]	61.8 (12.1)	61.9 (12.1)	61.8 (12.1)
≤65	1247 (58%)	1239 (58%)	2486 (58%)
>65	905 (42%)	913 (42%)	1818 (42%)
Race			
White	1124 (52%)	1166 (54%)	2290 (53%)
Black	104 (5%)	87 (4%)	191 (4%)
Asian	749 (35%)	718 (33%)	1467 (34%)
Native Hawaiian/Pacific Islander/ Native American/Alaskan	63 (3%)	75 (3%)	138 (3%)
Other	112 (5%)	106 (5%)	218 (5%)
Ethnicity			
Hispanic or Latino	522 (24%)	550 (26%)	1072 (25%)
Not Hispanic or Latino	1630 (76%)	1602 (74%)	3232 (75%)
Geographic Region[2]			
Asia	692 (32%)	654 (30%)	1346 (31%)
Europe	610 (28%)	623 (29%)	1233 (29%)
Latin/South America	449 (21%)	463 (22%)	912 (21%)
North America	401 (19%)	412 (19%)	813 (19%)
United States	268 (12%)	265 (12%)	533 (12%)
HbA1c (%) [1]	7.1 (2.0)	7.0 (2.0)	7.1 (2.0)
Type 2 Diabetes at Baseline [3]	1455 (67.6)	1451 (67.4)	2906 (67.5)
HbA1c (%) [1]	7.8 (1.7)	7.8 (1.6)	7.8 (1.7)
Systolic blood pressure (mmHg) [1]	136.7 (17.5)	137.4 (17.3)	137.1 (17.4)
Diastolic blood pressure (mmHg) [1]	77.5 (10.7)	77.5 (10.3)	77.5 (10.5)
Body mass index (kg/m^2) [1]	29.4 (6.0)	29.6 (6.3)	29.5 (6.2)
Baseline eGFR (mL/min/1.73 m^2)			
Mean (SD)	43.2 (12.3)	43.0 (12.4)	43.1 (12.4)
Median	41	42	41
< 30	293 (14%)	331 (15%)	624 (14%)
30 to < 45	979 (45%)	919 (43%)	1898 (44%)
45 to < 60	646 (30%)	682 (32%)	1328 (31%)
≥ 60	208 (10%)	200 (9%)	408 (9%)

	Dapagliflozin 10 mg (N=2152)	**Placebo (N=2152)**	**All (N=4304)**
Baseline UACR (mg/g)			
Mean (SD)	1370.6 (1200)	1356.4 (1200)	1363.5 (1200)
Median	960	930	950
≤ 1000	1104 (51%)	1121 (52%)	2225 (52%)
> 1000	1048 (49%)	1031 (48%)	2079 (48%)

1: Mean and standard deviation (in parenthesis) are presented. The remaining baseline variables are summarized using counts and percentages relative to N.
2: Asia included China, Indonesia, Japan, Korea, the Philippines, and Vietnam; Europe included Germany, Denmark, Spain, Great Britain, Hungary, Poland, Russia, Sweden, and the Ukraine; Latin America included Argentina, Brazil, Mexico, and Peru; North America included the United States and Canada.
3: Baseline diabetes was defined as a medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both Visit 1 and Visit 2.
Abbreviations: UACR=Urine albumin-to-creatinine ratio; HbA1c=glycated hemoglobin; eGFR=estimated glomerular filtration rate
Source: Clinical and Statistical reviewers

Common etiologies for chronic kidney disease included diabetic nephropathy, “chronic glomerulonephritis,” and ischemic/hypertensive nephropathy (Table 10). IgA nephropathy was the most common chronic glomerulonephritis. Additional demographic and baseline characteristics for the common etiologies of CKD are further described in the appendix (Table 50 to Table 52).

Table 10 CKD Etiologies of Randomized Patients

	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)	All (N=4304)
Diabetic nephropathy	1271 (59%)	1239 (58%)	1271 (59%)
Chronic glomerulonephritis	343 (16%)	352 (16%)	695 (16%)
Biopsy-confirmed	225 (10%)	237 (11%)	462 (11%)
Subtypes [1]			
IgA nephropathy	137 (6%)	133 (6%)	270 (6%)
FSGS	53 (2%)	62 (3%)	115 (3%)
Membranous nephropathy	19 (<1%)	24 (1%)	43 (<1%)
Minimal change	7 (<1%)	4 (<1%)	11 (<1%)
Other glomerulonephritis	127 (6%)	129 (6%)	256 (6%)
Ischemic/hypertensive nephropathy	324 (15%)	363 (17%)	687 (16%)
Unknown	110 (5%)	104 (5%)	214 (5%)
Chronic pyelonephritis (infectious)	30 (1%)	39 (2%)	69 (2%)
Chronic interstitial nephritis	33 (2%)	20 (<1%)	53 (1%)
Other	22 (1%)	19 (<1%)	41 (<1%)
Obstructive nephropathy	13 (<1%)	12 (<1%)	25 (<1%)
Renal artery stenosis	6 (<1%)	4 (<1%)	10 (<1%)

Counts and percentages in parenthesis are presented.
1: Do not necessarily reflect biopsy-confirmed diagnoses.
Abbreviations: FSGS=focal segmental glomerulosclerosis; IgA=immunoglobin; CKD: chronic kidney disease
Source: Clinical and Statistical reviewers

Among patients with T2DM at baseline, the most common cause of CKD was reported as diabetic nephropathy, followed by ischemic/hypertensive nephropathy (Figure 24 in the appendix).

Reviewer's comment: (b) (4) *we wanted to better understand the breadth of the CKD etiologies in the trial. To do so, we evaluated how the CKD diagnosis was ascertained, and performed a more granular review of less descriptive groupings of CKD etiologies, such as "other" and "other glomerulonephritis."*

The enrollment form was designed to systematically capture a single diagnosis of CKD from a predefined list and to indicate whether the diagnosis was presumptive or based on a kidney biopsy (sample electronic case report form [eCRF] is shown in Figure 22 in appendix). In an information request dated January 22, 2021, the Applicant provided an analysis of CKD etiologies confirmed by biopsy; see Figure 25 (in the appendix) and Table 47. This analysis showed that 80% of patients had a presumptive diagnosis, while 20% had a biopsy confirmed diagnosis. The most common biopsy-confirmed etiology was a glomerulonephritis.

The Applicant clarified that only one CKD etiology category was recorded per randomized patient. The investigator was instructed to choose the most likely etiology from a list. In instances where the investigator selected multiple etiologies or chose the option "other," the investigator was asked to choose one etiology, if a single etiology could not be ascertained, then the etiology was coded as "other" and the investigator was allowed to fill in a free text field.

A nephrologist manually reviewed the free-text categories entered by investigators for the category "other." This revealed that, of the 41 cases in this category, most were due to "unclear etiology" followed by "tubulointerstitial nephritis" (see Table 48 in appendix). Although the exclusion criteria specified the exclusion of patients with polycystic kidney disease, there was one patient enrolled with this diagnosis.[39] A small number of patients had a form of hereditary nephropathy. Ten cases in the "other" category had at least two etiologies of CKD recorded, most of them were a combination of diabetes mellitus and hypertension. [40]

The Applicant also reviewed the information for the 256 patients in the "other glomerulonephritis" category; 214 were further categorized as "no specified type of glomerulonephritis" because of an absence of a kidney biopsy (189 patients), and, for the remaining 25, a single type of glomerulonephritis could not be verified despite a kidney biopsy. Of the patients with an identified etiology, the most common was categorized as "immunoglobulin and complement-mediated"; see Table 49 in appendix. This table shows small numbers of a broad distribution of CKD etiologies, including some rare diseases, such as Alport syndrome (reported in 6 patients).

The Applicant was also asked to provide additional details regarding the basis for diagnosis of "chronic glomerulonephritis" for the 233 (33.5%) patients without a reported kidney biopsy. On March 26, 2021, the Applicant clarified that in the majority of cases, the free text field simply stated that a "diagnosis could not be verified without kidney biopsy taken" (189 patients), or that the diagnosis was "based solely on clinical judgement and kidney biopsy was not deemed necessary" (10 cases); no additional information was available for the remaining 34 patients without a biopsy. Because, clinically, a kidney biopsy is generally considered necessary to make a diagnosis of glomerulonephritis, the subgroup analysis for these patients includes only patients with a biopsy (see Figure 5).

In sum, the trial enrolled a broad range of CKD etiologies. Not surprisingly, the most common etiologies of chronic kidney disease, (i.e., diabetic nephropathy and ischemic/hypertensive nephropathy), make up three fourths of the patients randomized. The trial also captured other

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[39] Subject identifier (b) (6) was randomized to placebo and had an "other" diagnosis of "polycystic kidney disease"

[40] Diabetic nephropathy and ischemic hypertensive nephropathy were identified in six cases. The remaining cases included: (b) (6) - "nephrolithiasis, nephrectomy, chronic glomerulonephritis, secondary ischemic glomerulopathy"; (b) (6) - "diabetic nephropathy + IgA nephropathy"; (b) (6) - " mixed nephropathy (hypertensive+goiter); (b) (6) - "gouty nephropathy, chronic pyelonephritis (infectious), diabetic nephropathy"

less common causes of CKD.

Table 11 shows common baseline comorbidities, which were generally well balanced between treatment arms. Hypertension (96%), dyslipidemia (69%), and type 2 diabetes (67%) were the most common comorbidities.

Table 11 Past medical history reported for greater than 5% of randomized patients

Dictionary-Derived Term; N (%)	Dapagliflozin 10mg N=2152	Placebo N=2152	All N=4304
Hypertension	2065 (96%)	2056 (96%)	4121 (96%)
Dyslipidemia	1488 (69%)	1500 (70%)	2988 (69%)
Type 2 diabetes mellitus	1444 (67%)	1442 (67%)	2886 (67%)
Neuropathy peripheral	470 (22%)	482 (22%)	952 (22%)
Gout	384 (18%)	388 (18%)	772 (18%)
Cardiac failure	235 (11%)	233 (11%)	468 (11%)
Coronary artery stenosis	216 (10%)	216 (10%)	432 (10%)
Angina pectoris	201 (9%)	204 (9%)	405 (9%)
Myocardial infarction	185 (9%)	207 (10%)	392 (9%)
Peripheral arterial occlusive disease	154 (7%)	171 (8%)	325 (8%)
Sleep apnea syndrome	141 (7%)	154 (7%)	295 (7%)
Percutaneous coronary intervention	145 (7%)	149 (7%)	294 (7%)
Ischemic stroke	125 (6%)	140 (6%)	265 (6%)
Atrial fibrillation	110 (5%)	107 (5%)	217 (5%)

Source: ADMH.xpt dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

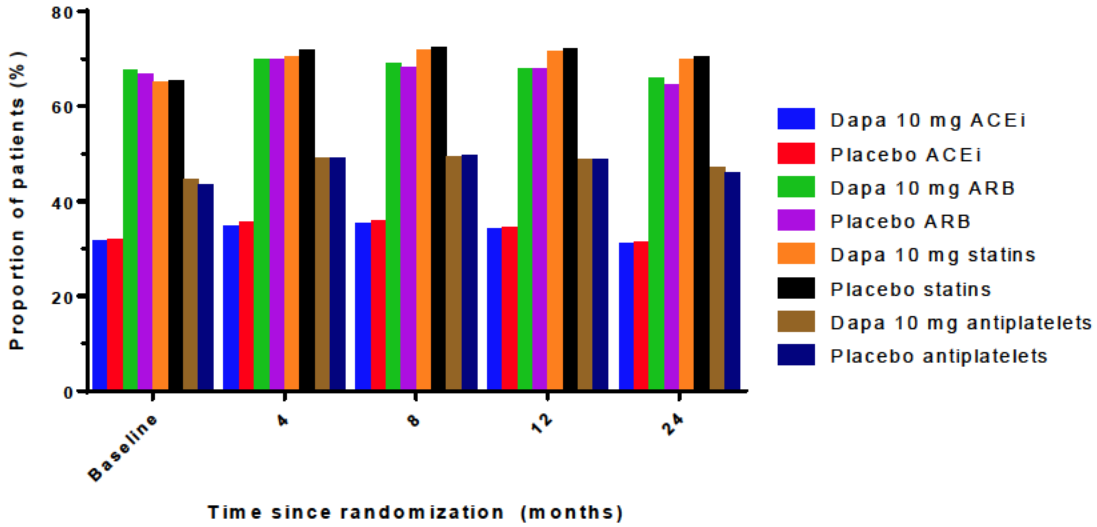
Compliance with study drug was assessed by pill counts.[41] Approximately 84% of randomized patients had adequate data for assessment of compliance. Compliance was similar in both treatment groups (96% to 99%).

Concomitant medications were captured at baseline and each study visit. Figure 3 shows the use of ACEi, ARBs, statins, and antiplatelet medications at baseline and throughout the study. Overall, 97% of patients were taking either an ACEi or ARB at randomization. The use of ACEi, ARBs, statins, and antiplatelets agents at baseline was 31%, 66%, 65%, and 43%, respectively. Review of concomitant medications throughout the study did not reveal any clinically important differences between treatment arms.

[41] The calculations for compliance were derived from the number of pills taken divided by the expected number of pills taken from first dose date to last dose date. If the number of tablets dispensed or the number of tablets returned was missing for at least one observation, compliance was not calculated for that patient.

For patients with a history of T2DM, use of diabetes medications at randomization was also well balanced between treatment arms. Approximately 94% of patients in each treatment group used any diabetes medication. Insulin[42] was the most common therapy used by patients with T2DM, followed by biguanides.[43]

Figure 3 Concomitant CKD and CV medications of interest over time



Abbreviations: CKD=chronic kidney disease; CV=cardiovascular; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; Dapa=dapagliflozin
Source: Clinical reviewer graphed data from CSR table 14.1.5.5

Reviewer's comments: In accordance with FDA advice, the protocol provided investigators guidance to ensure that patients receive standard of care treatments for CKD, T2DM, and CV risk factors. In addition, based on the DMC and EC minutes, there appeared to be adequate monitoring of the use of CKD and CV medications in this population. During the October 16, 2018 open DMC meeting, the DMC noted that the use of lipid-lowering and antithrombic therapies might be lower than expected. In response, the EC evaluated the use of these therapies from similar published trials and concluded that, when considering only the patients with T2DM, the use of these therapies in DAPA-CKD was similar to use in other trials. In addition, the EC emphasized that the population enrolled in DAPA-CKD was broader than similar kidney outcomes trials, which enrolled patients with diabetic kidney disease.

[42] Insulin was used by 814 patients randomized to dapagliflozin (approximately 56.4% of 1,444 patients with T2DM) and 784 patients randomized to placebo (approximately 54.4% of the 1,442 of the patients with T2DM).
[43] Biguanides were used by 629 patients randomized to dapagliflozin (approximately 43.6% of 1,444 patients with T2DM) and 613 patients randomized to placebo (approximately 42.5% of 1,442 patients with T2DM).

Use of prohibited medications
Version 2 of the protocol clarified that patients should not use open-label SGLT2 inhibitors during the trial. Per review of the concomitant medication dataset, 34 (0.8%) patients equally distributed between the dapagliflozin and placebo groups were treated with an open-label SGLT2 inhibitor. Two patients stopped study drug (see Table 6), and 14 patients were reported as having an important protocol deviation (Table 8).

Reviewer's comment: Despite concerns for open label use of SGLT2 inhibitors, there were few patients who took an open-label SGLT2 inhibitor during the trial, and they were balanced between the treatment arms; therefore, it is not likely that use of an open-label SGLT2 inhibitor impacted the efficacy findings.

Efficacy Results – Primary Endpoint

The primary endpoint was a composite of a sustained ≥ 50% decline in eGFR, ESKD, and renal or CV death. Patients in the dapagliflozin arm experienced fewer primary endpoint events compared to patients in the placebo arm (197 vs. 312; HR 0.61 [95% CI 0.51-0.72; p < 0.0001]) (Table 12). All individual components contributing to the primary efficacy endpoint were numerically lower on dapagliflozin compared with placebo, although there were few renal deaths. The Kaplan-Meier curves for the composite primary endpoint separated around month 4 and continued to diverge during the study period (Figure 4).

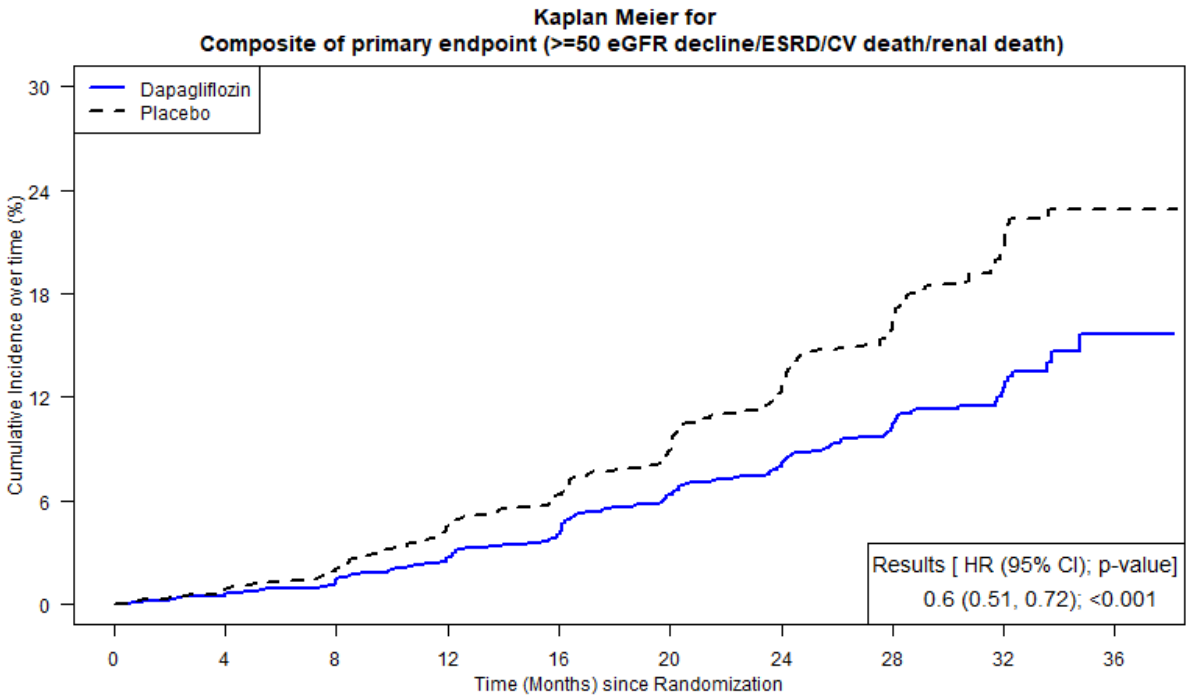
Analyses of the individual components of the primary endpoint regardless of the other components were supportive (Table 12 and Figure 26 to Figure 30 in the Appendix). In particular, time to a sustained ≥50% decline eGFR, time-to-first ESKD, time-to-first sustained eGFR<15 ml/min/1.73m^2, and time to chronic dialysis regardless of the other components were all nominally statistically significant and favored dapagliflozin compared to placebo arm.

Table 12 Primary efficacy analysis (FAS)

	Dapagliflozin 10 mg (N=2152)		Placebo (N=2152)		Hazard Ratio (95% CI); p-value [3]
	Event (%) [1]	Event Rate [2]	Events (%) [1]	Event Rate [2]	
Primary Composite Endpoint [4]	197 (9.2%)	4.6	312 (14.5%)	7.5	0.61 (0.51, 0.72); <0.0001
Sustained ≥ 50% decline in eGFR	59 (2.7%)		133 (6.2%)		
ESKD	83 (3.9%)		108 (5.0%)		
Sustained eGFR<15 [5]	58 (2.7%)		76 (3.5%)		
Chronic dialysis	25 (1.2%)		32 (1.5%)		
Kidney transplant	-		-		
Renal death	-		2 (0.1%)		
CV death	55 (2.6%)		69 (3.2%)		
Individual Components					
Sustained ≥ 50% decline in eGFR	112 (5.2%)	2.6	201 (9.3%)	4.8	0.53 (0.42, 0.67)
ESKD	108 (5.0%)	2.5	161 (7.5%)	3.8	0.64 (0.50, 0.82)
Sustained eGFR<15 [5]	83 (3.9%)	1.9	120 (5.6%)	2.8	0.67 (0.51, 0.88)
Chronic dialysis	68 (3.2%)	1.5	99 (4.6%)	2.2	0.66 (0.48, 0.90)
Kidney transplant	3 (0.1%)	0.1	8 (0.4%)	0.2	0.35 (0.09, 1.32)
Renal death	2 (0.1%)	0.0	6 (0.3%)	0.1	0.34 (0.07, 1.70)
CV death	65 (3.0%)	1.4	80 (3.7%)	1.7	0.81 (0.58, 1.12)

1: Total number of events and the percentage of events relative to N in parenthesis
2: Event rate is per 100 patient years where a month consists of 30 days.
3: Hazard ratio, respective 95% CI, and Wald-based p-value from Cox proportional hazards model adjusting for continuous baseline eGFR stratified by baseline factor. Differs from Applicant where the p-value is obtained from a Score test (see statistical method section). P-values are not reported for the individual components.
4: For the components of the composite primary endpoint, tie-breaking of the event contributing to the endpoint is based on the following hierarchy in the following order: eGFR < 15, eGFR ≥ 50% decline from baseline, chronic dialysis, kidney transplant, death
5: eGFR in ml/min/1.73m^2
Abbreviations: eGFR=estimated glomerular filtration rate; ESKD=end-stage renal disease; CV=cardiovascular; adj=adjudicated; CI=confidence interval; PH=proportional hazards
Source: Statistical reviewer

Figure 4 Kaplan-Meier plot of the primary efficacy analysis- composite of >= 50% eGFR decline, ESKD, and renal or CV death- FAS



Number of Events										
Dapagliflozin	0	12	29	53	80	122	150	176	191	197
Placebo	0	18	42	91	125	174	231	278	306	312
Number at Risk										
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309	31
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270	24
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.6	1.4	2.7	4.1	6.3	8.0	10.2	12.6	15.7
$\hat{F}_{Placebo}$	0.0	0.9	2.1	4.6	6.3	9.0	12.4	16.3	20.8	22.8

Source: Statistical reviewer

Reviewer's comment: We reviewed a random sample primary endpoint events. In general, the events captured clinically meaningful events that met the prespecified definitions (see Table 45 in the appendix for definitions). Below is a summary of the events reviewed:

1. *We reviewed events that were programmatically identified and reported by the central laboratory that were not adjudicated. These events included: sustained eGFR <15 mL/min/1.72m^2 and ≥50% sustained decline in eGFR.*

   Per the CEA charter and study protocol, a sustained decline in eGFR of ≥50% was defined as a decline from baseline on two consecutive central laboratory eGFR values at least 28 days apart. A sustained eGFR <15 mL/min/1.72m^2 was defined by the study protocol and CEA charter, as two consecutive central laboratory eGFR values <15 mL/min/1.73m^2 at least 28 days apart.

   The CEA charter, study protocol, and SAP, did not explicitly state how values obtained in the intervening 28 day period would be handled; however, according to the Analysis

Data Reviewer's Guide, "if there is one or more intermediate value between 1 and 28 days that does not meet the criteria, then the decline is not sustained. If no intermediate value, or all intermediate values meet the criteria, then the decline is sustained if the first value beyond 28 days meets the criteria." This is the approach generally recommended to handle intervening eGFR values in such analyses.

- *We reviewed eGFR trends for ten randomly selected cases of a sustained decline in eGFR of ≥50% and ten randomly selected cases of a sustained eGFR<15 mL/min/1.72m^2 (see Appendix section 12.7). All cases showed a steady decline in eGFR over time. One subject experiencing a ≥50% decline in eGFR seemed to have a spuriously elevated baseline eGFR value, which may have affected when the ≥50% cut off was met, but, given the continued decline in eGFR in this patient, this did not affect the clinical importance of this event. The overall eGFR trends for the cases reviewed appeared to capture persistent decreases in eGFR and not transient eGFR variations.*

2. *We also reviewed five randomly selected chronic dialysis and two kidney transplant cases (see Appendix section 12.7).*
    - *Chronic dialysis events and the reason (i.e., acute kidney injury or progression of underlying chronic kidney disease) were adjudicated and defined as treatment ongoing for at least 28 days or stopping dialysis before 28 days due to death, futility, or patient electing to stop dialysis where the renal deterioration was deemed irreversible. Four of the cases reviewed had dialysis ongoing for ≥28 days, which was verified during the adjudication process (i.e., by querying the investigator or by the investigator documenting in the eCRF that dialysis was ongoing after 90 days [one case]). One chronic dialysis case had a duration of less than 28 days. In that case, dialysis was initiated during an episode of progressively worsening dyspnea requiring mechanical ventilation, and the patient died before reaching Day 28. Based on the overall eGFR trend before the patient's hospitalization/dialysis, it seems likely that the kidney failure was irreversible. In summary, all reviewed cases appeared to capture irreversible kidney failure requiring chronic dialysis.*
    - *All kidney transplantation events were adjudicated. Events were identified by the date of transplantation or by patients with perioperative death at kidney transplantation. We reviewed two cases, both of which provided adequate evidence of kidney transplantation.*

3. *We reviewed a randomly selected sample of two renal death events and five CV death events.*
    - *Renal death was defined as death due to ESKD after deliberately withholding of dialysis treatment for any reason (i.e., patient refusing dialysis, care provider considering dialysis futile, or dialysis not being available). Deaths related to causes other than ESKD were not to be adjudicated as renal death. We agree*

with the classification of the randomly selected cases as renal deaths (see Appendix section 12.7)

- *The CEA had specific criteria for the adjudication of CV deaths (see Table 45). For the purposes of the primary and secondary endpoints, the SAP included deaths adjudicated as "undetermined deaths" in the analysis of CV deaths. Overall, we agree with the classification of the randomly selected cases as CV deaths (see Appendix section 12.7).*

Sensitivity Analyses

A total of 827 patients were included in a multiple imputation analysis to evaluate the potential impact of missing data on the primary efficacy findings (817 patients were censored prematurely due to missing eGFR assessments and 10 due to withdrawal of consent). Using a retrieved dropout approach, the imputed results (HR: 0.73; 95% CI 0.62, 0.86) were consistent with the conclusion of the primary efficacy endpoint.

The Applicant provided a second analysis using a hazard rate estimated according to patients' on-treatment and off-treatment status. This estimated HR was 0.68 (95% CI 0.58, 0.81), favoring the dapagliflozin arm and consistent with the conclusion of the primary efficacy findings.

In addition, the statistical reviewer conducted a tipping point analysis using the Applicant's second analysis as a starting point and the findings were robust to deviations of missing data assumptions (Figure 36).

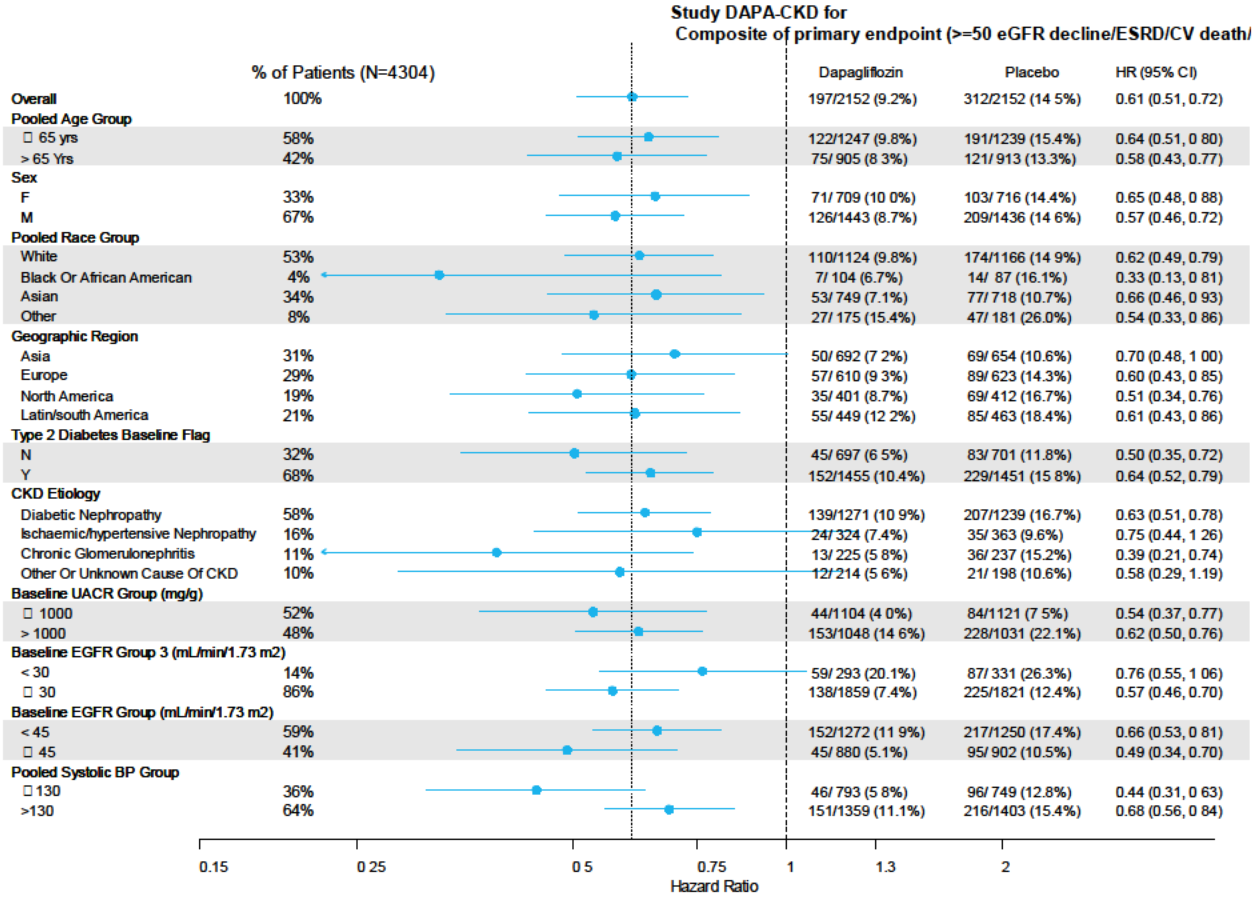
In summary, the primary efficacy results were robust to missing data assumptions.

Subgroup Analyses

Subgroup analyses for the primary efficacy endpoint were consistent across subgroups defined by demographic and baseline characteristics, presence or absence of T2DM, and various CKD etiologies (including diabetic nephropathy, ischemic/hypertensive nephropathy, chronic glomerulonephritis [including only biopsy-proven diagnoses],[44] and other or unknown cause of CKD. All analyses favored dapagliflozin over placebo (Figure 5).

[44] We considered patients with a biopsy-proven diagnosis of glomerulonephritis, given that a diagnosis of glomerulonephritis generally requires a histological assessment for diagnosis. This analysis excluded 233 patients classified as having "chronic glomerulonephritis" without a biopsy. We also explored the primary efficacy findings in the subgroup of patients diagnosed with chronic glomerulonephritis regardless of biopsy status, and the findings were similar to those shown in Figure 5.

Figure 5 Forest plot of the composite of ≥ 50% eGFR decline, ESKD, renal death or CV death by subgroups (FAS)

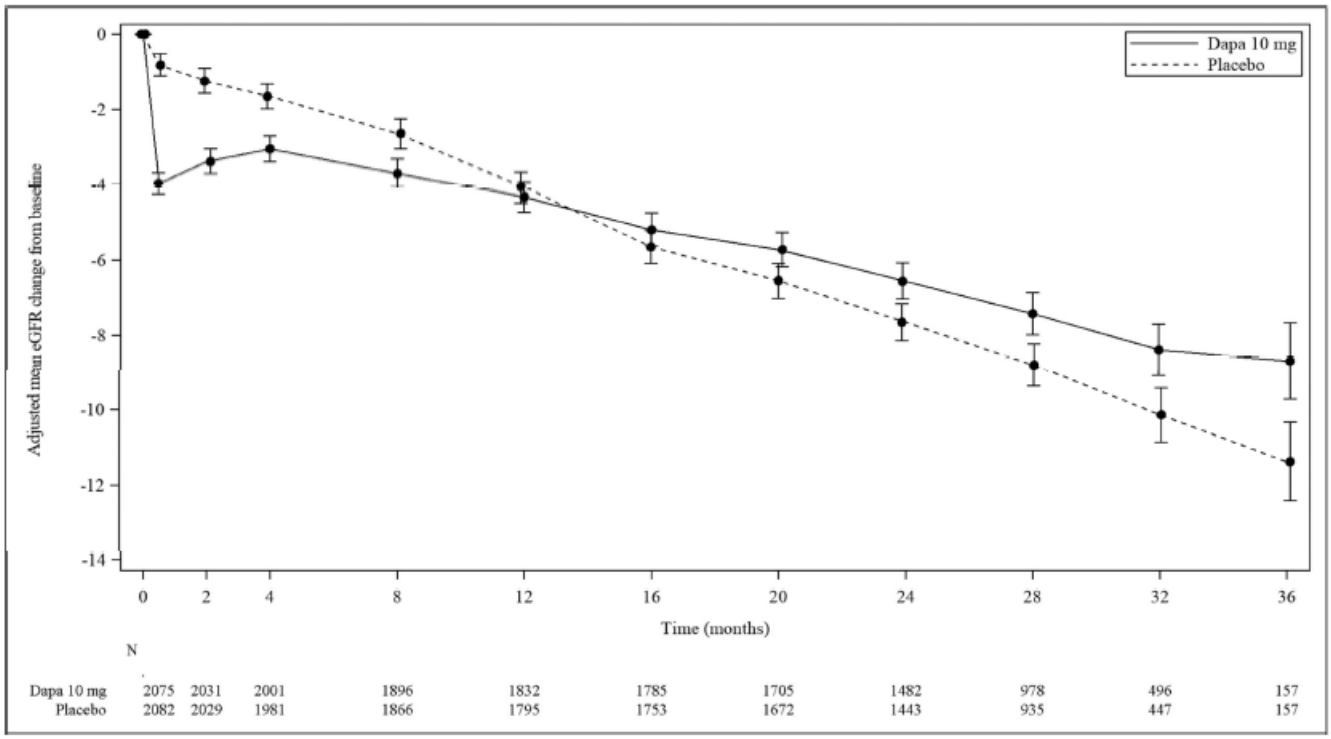


n/N(%): The total number of first events/number of randomized patients and percentage of randomized patients with the first events are presented by arm.
The estimated hazard ratio and respective 95% confidence intervals are based on a stratified Cox proportional hazards model adjusting for treatment group and baseline continuous eGFR conducted within levels of the subgroups.
For subgroup analysis of Type 2 diabetes baseline flag, stratum consist only of high or low UACR.
For subgroup analysis of baseline UACR, stratum consists only of baseline Type 2 diabetes.
For the CKD etiology, only patients with a biopsy confirmed diagnosis at baseline were included in the analysis for the "Chronic Glomerulonephritis" subtype.
Abbreviations: eGFR=estimated glomerular filtration rate; CV=cardiovascular; CKD=chronic kidney disease; BP=blood pressure; F=female; M=male; N=no; Y=yes, HR=hazard ratio; CI=confidence intervals
Source: Statistical reviewer

Change in eGFR

Figure 6 shows the Applicant's analysis of the adjusted mean change from baseline of eGFR over time using repeated measures. After an initial acute decrease in eGFR in the dapagliflozin arm, the rate of eGFR decline appears to be slower in the dapagliflozin arm compared with the placebo arm. We note, however, that few patients contributed data at later timepoints.

Figure 6 Adjusted mean eGFR (CKD-EPI) Change from Baseline and 95% CIs from repeated measures model (FAS)



The repeated measures model includes terms for randomised treatment group, baseline measurement, visit and visit by treatment group interaction.
The repeated measures model includes all windowed eGFR values through to 36 months that occur on or after first dose of study drug and on or before last dose of study drug. N is the number of patients at each visit. 1 month corresponds to 30 days.

CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; Dapa, dapagliflozin; FAS, full analysis set; eGFR, estimated glomerular filtration rate

Source: CSR, Figure 13.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoint: Renal composite endpoint

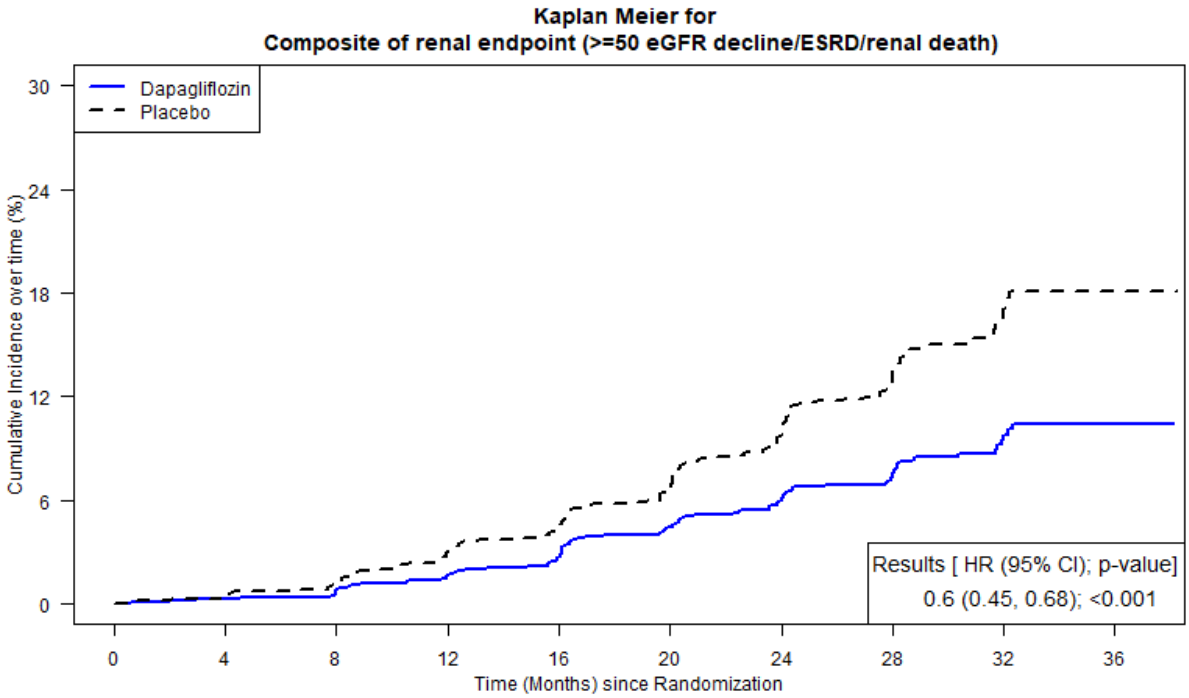
The first secondary endpoint was the time to the first occurrence of the following composite: sustained decline in eGFR of at least 50%, ESKD (defined as a sustained eGFR<15 mL/min/1.73m^2, chronic dialysis treatment, kidney transplant), or renal death. As shown in Table 13, fewer patients in the dapagliflozin arm experienced an event (adjusted HR 0.56 [95% CI: 0.45, 0.68; p<0.0001]) compared to patients in the placebo arm. The Kaplan-Meier curves further separated over time (Figure 7).

Table 13 Time-to-first sustained decline of at least 50% in eGFR, ESKD or Renal Death

Endpoint	Dapagliflozin 10 mg (N=2152)		Placebo (N=2152)		HR (95% CI); p-value[3]
	Event (%) [1]	Event Rate [2]	Event (%) [1]	Event Rate [2]	
Decline of eGFR by 50%, ESKD, renal death	142 (6.6%)	3.4	243 (11.3%)	5.9	0.56 (0.45, 0.68); <0.0001
Decline eGFR by 50%	59 (2.7%)		133 (6.2%)		
ESKD	83 (3.9%)		108 (5.0%)		
Sustained eGFR<15	58 (2.7%)		76 (3.5%)		
Chronic Dialysis	25 (1.2%)		32 (1.5%)		
Renal death	-		2 (0.1%)		

1: Total number of events and the percentage of events relative to N in parenthesis
2: Event rate is per 100 patient years where a month consists of 30 days.
3: Hazard ratio, respective 95% CI, and Wald-based p-value from Cox PH model adjusting for continuous baseline eGFR stratified by baseline factor. Differs from Applicant where the p-value is obtained from a Score test.
4: The unit for eGFR is mL/min/1.73 m^2
Source: Statistical reviewer

Figure 7 Kaplan-Meier Plot of Composite of ≥ 50% eGFR Decline, ESKD and Renal Death (FAS)



Number of Events										
Dapagliflozin	0	6	16	32	52	85	109	125	140	142
Placebo	0	10	25	61	89	129	179	217	240	243
Number at Risk										
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309	31
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270	24
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.3	0.8	1.6	2.7	4.4	5.9	7.3	9.8	10.4
$\hat{F}_{Placebo}$	0.0	0.5	1.2	3.1	4.6	6.8	9.9	13.1	17.1	18.1

Abbreviations: eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

Secondary endpoint: CV death and HHF composite endpoint

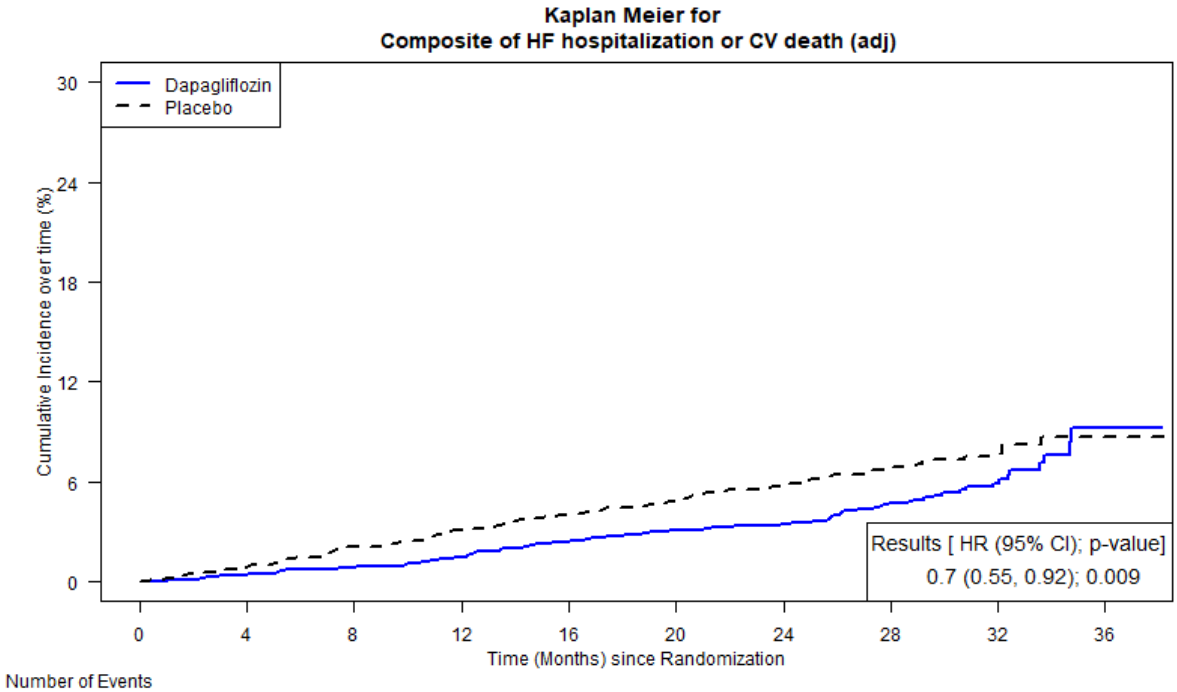
The next secondary endpoint in the hierarchical testing sequence was the composite of CV death or hospitalization for heart failure. As shown in Table 14, fewer patients in the dapagliflozin arm experienced an event compared with patients in the placebo arm (adjusted hazard ratio 0.71 [95% CI: 0.55, 0.92; p=0.009]). The finding was driven by first events of hospitalization for heart failure. As noted in Table 12, there were also numerically fewer CV deaths overall. The Kaplan-Meier curves separated early in the trial. Although the curves converged around Month 36, fewer than 100 patients reached that duration of follow-up (Figure 8).

Table 14 Time to composite of CV death and hospitalization for heart failure (FAS)

Endpoint	Dapagliflozin 10 mg (N=2152)		Placebo (N=2152)		HR (95% CI); p-value [3]
	Event (%) [1]	Event Rate	Event (%) [1]	Event Rate	
CV death and HHF	100 (4.6%)	2.2	138 (6.4%)	3.1	0.71 (0.55, 0.92); 0.009
CV death	63 (2.9%)		67 (3.1%)		
HHF	37 (1.7%)	0.8	71 (3.3%)	1.6	0.5 (0.34, 0.76); <0.001

1: Total number of first events and the percentage of first events relative to N in parenthesis
2: Event rate is per 100 patient years where a month consists of 30 days.
3: Hazard ratio, respective 95% CI, and Wald-based p-value from Cox PH model adjusting for continuous baseline eGFR stratified by baseline factor. Differs from Applicant where the p-value is obtained from a Score test.
Abbreviations: HHF=hospitalization for heart failure; CV=cardiovascular; HR=hazard ratio; CI=confidence intervals; FAS=full analysis set
Source: Statistical reviewer

Figure 8 Kaplan-Meier Plot of Composite of CV death and HHF (FAS)



Number of Events										
Dapagliflozin	0	9	17	29	49	62	69	85	93	100
Placebo	0	19	42	63	82	97	115	128	135	138
Number at Risk										
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384	41
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360	44
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.4	0.8	1.4	2.4	3.0	3.4	4.7	5.9	9.2
$\hat{F}_{Placebo}$	0.0	0.9	2.0	3.1	4.0	4.8	5.8	6.7	7.7	8.7

Abbreviations: CV=cardiovascular; HHF=hospitalization for heart failure; HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

Reviewer's comments: We reviewed a random sample of cases adjudicated as a heart failure hospitalization and concluded that the adjudication of these events was consistent with the CEA charter event definitions; see Section 12.7 for a sample of narratives reviewed. Overall, the findings that dapagliflozin reduces the risk of hospitalization of heart failure are consistent with the previously labeled findings based on the DECLARE and DAPA-HF trials.

Secondary endpoint: Death from any cause

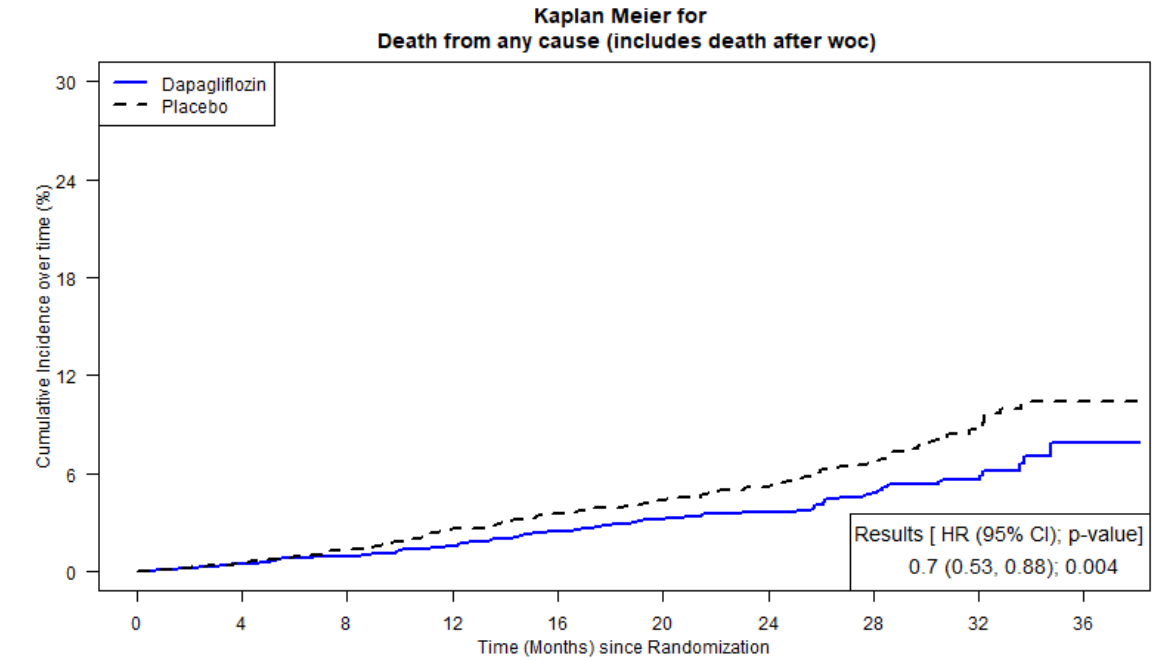
At the time of database lock, fewer patients had died in the dapagliflozin arm (101 total, event rate of 2.2 per 100 patient-years) compared with patients in the placebo arm (146 total, event rate of 3.2 per 100 patient-years). The adjusted hazard ratio for death was 0.69 (95% CI: 0.53, 0.88; p=0.004) (Table 15). The Kaplan-Meier curves continued to diverge over time, although fewer than 100 patients were followed through Month 36 (Figure 9).

Table 15 Time to all-cause death (FAS)

Endpoint	Dapagliflozin 10 mg (N=2152)		Placebo (N=2152)		HR (95% CI); p-value [3]
	Event (%) [1]	Event Rate [2]	Event (%) [1]	Event Rate [2]	
All Cause Death	101 (4.7%)	2.2	146 (6.8%)	3.2	0.69 (0.53, 0.88); 0.004

1: Total number of first events and the percentage of first events relative to N in parenthesis
2: Event rate is per 100 patient years where a month consists of 30 days.
3: Hazard ratio, respective 95% CI, and Wald-based p-value from Cox PH model adjusting for continuous baseline eGFR stratified by baseline factor. Differs from Applicant where the p-value is obtained from a Score test.
Abbreviations: HR=hazard ratio; CI=confidence intervals; FAS=full analysis set
Source: Statistical reviewer

Figure 9 Kaplan-Meier plot of death from any cause (FAS)



Abbreviations: HR=hazard ratio; CI=confidence interval; woc=withdrawal of consent; FAS=full analysis set
Source: Statistical reviewer

A total of 18 deaths occurred between 5 and 67 days after the PACD, five in the dapagliflozin arm and 13 in the placebo arm. Inclusion of these deaths in the analysis did not affect the conclusion (HR: 0.66; 95%CI: 0.52, 0.85).

Causes of Death

Patients in the dapagliflozin arm experienced fewer CV, non-CV, and undetermined causes of death as compared to patients in the placebo arm (Table 16). The differences in different sub-categories of death were small. The largest difference in CV deaths was due to heart failure, which affected eight (0.4%) additional patients in the placebo arm compared with dapagliflozin. The difference in non-CV deaths was attributed primarily to a difference in infections (additional 10 patients [0.5%] in the placebo arm) and malignancy (additional 11 [0.5%] patients in the placebo arm). PT terms associated with infection-related deaths suggest the findings were primarily driven by preferred terms for pneumonia[45] and sepsis/septic shock.[46] The malignancy findings were predominantly driven by PT terms for lung neoplasm. [47] Additional information can be found in Table 58 and Table 53 in the appendix.

[45] When considering the PT terms "pneumonia" and "pneumonia bacterial" together, there are 3 (0.1%) and 9 (0.4%) patients randomized to dapagliflozin and placebo, respectively (see Table 58 in appendix)

[46] When considering the PT terms "sepsis" and "septic shock" together, there are 6 (0.3%) and 14 (0.7%) patients randomized to dapagliflozin and placebo, respectively (see Table 58 in appendix).

[47] When considering the PT terms "lung neoplasm," "lung neoplasm malignant," "Non-small cell lung cancer," and "small cell lung cancer" together, there are 2 (0.1%) and 6 (0.3%) patients randomized to dapagliflozin and placebo, respectively (see Table 58 in appendix).

Table 16 Deaths classified by adjudication categories

	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
All deaths	101 (4.7)	146 (6.8)	247 (5.7)
CV deaths	41 (1.9)	50 (2.3)	91 (2.1)
Death due to acute myocardial infarction	6 (0.3)	5 (0.2)	11 (0.3)
Sudden cardiac death	24 (1.1)	27 (1.3)	51 (1.2)
Death due to heart failure	3 (0.1)	11 (0.5)	14 (0.3)
Death due to stroke	5 (0.2)	5 (0.2)	10 (0.2)
Death due to CV procedures	0	1 (<0.1)	1 (<0.1)
Death due to CV hemorrhage	1 (<0.1)	0	1 (<0.1)
Death due to other CV cause	2 (0.1)	1 (<0.1)	3 (0.1)
Non-CV death	36 (1.7)	66 (3.1)	102 (2.4)
Pulmonary failure	3 (0.1)	1 (<0.1)	4 (0.1)
Renal	2 (0.1)	6 (0.3)	8 (0.2)
Gastrointestinal causes	2 (0.1)	2 (0.1)	4 (0.1)
Hepatobiliary	0	3 (0.1)	3 (0.1)
Infection (includes sepsis)	18 (0.8)	28 (1.3)	46 (1.1)
Hemorrhage neither CV bleeding nor stroke	0	4 (0.2)	4 (0.1)
Trauma	3 (0.1)	1 (<0.1)	4 (0.1)
Suicide	0	1 (<0.1)	1 (<0.1)
Malignancy	8 (0.4)	19 (0.9)	27 (0.6)
Other	0	1 (<0.1)	1 (<0.1)
Undetermined cause of death	24 (1.1)	30 (1.4)	54 (1.3)

Abbreviations: CV=cardiovascular
Source: Modified Table 14 from CSR. Table includes deaths prior to primary analysis censoring date only, as per SAP. Subject (b) (6), who died after withdrawal of consent, was not included in this summary as the death was not submitted for adjudication

Reviewer's comments: The most common causes of death in patients with CKD are CV death, cancer, and infections, consistent with the findings in DAPA-CKD.[48] Although there are slight numerical differences in cancer and infection as causes of non-CV deaths, there is no clear mechanistic explanation for the treatment differences.

Sensitivity Analyses for Secondary Endpoints

Subgroup findings for secondary endpoints were generally consistent across key subgroups (Figure 31 to Figure 34 in the appendix). The one exception was that the ischemic/hypertensive nephropathy subgroup for the secondary endpoint CV death and hospitalization for heart

[48] Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, et al. Cause of death in patients with reduced kidney function. Journal of the American Society of Nephrology. 2015;26(10):2504.

failure favored placebo; however, we believe this is most likely a spurious finding due to the small number of events in this subgroup (17 dapagliflozin and 15 placebo).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Two patient-reported outcomes (PROs) assessments were administered during DAPA-CKD: the Kidney Disease Quality of Life-36 (KDQOL 36) and the EuroQol five-dimensional five-level questionnaire (EQ-5D-5L).

For the KDQOL-36, the Applicant cited 3 to 5 points as a clinically relevant change/difference. The treatment arms were well balanced for KDQOL-36 scores at baseline. At 12, 24, and 36 months, there were no relevant changes compared to baseline and no clinically relevant differences between dapagliflozin and placebo (Table 55).

The EQ-5D-5L is a self-reported questionnaire to measure heath status that includes of five dimensions, which when analyzed together, produce the EQ-5D index and the EQ VAS (a visual analogue scale). In general, similar results were observed across categories of the instrument for dapagliflozin and placebo (Table 56).

Reviewer's comment: Because this was an event-driven study, only 47% of patients had a PRO assessment at 36 months at study closeout.

7.1.3. DECLARE: Dapagliflozin Effect on Cardiovascular Events (DECLARE): (study code: D1693C00001)

(b) (4) The DECLARE study has been previously reviewed by the FDA; therefore, this section provides a high-level overview of aspects of the trial (b) (4) [49]

Relevant Regulatory History

The study results for DECLARE were submitted for FDA review on December 18, 2018 to support two new indications (NDA 202293, supplement 18). The first was a reduction in hospitalization for heart failure in T2DM; (b) (4)

[49] FDA reviews for NDA 202293 S-018: Clinical review authored by Michelle Carey dated October 15, 2019; Division Summary Memo for Regulatory action and CDTL review dated October 18, 2019 authored by Patrick Archdeacon; Statistical Review and Evaluation authored by Yun Wang dated October 1, 2019; and consult from the Division of Cardiovascular and Renal Products authored by Kimberly Smith dated October 15, 2019.

(b) (4)

Based on the DECLARE results, the FDA granted an indication for dapagliflozin for a reduction in the risk of hospitalization for heart failure in adults with T2DM and established CV disease or multiple CV risk factors. (b) (4)

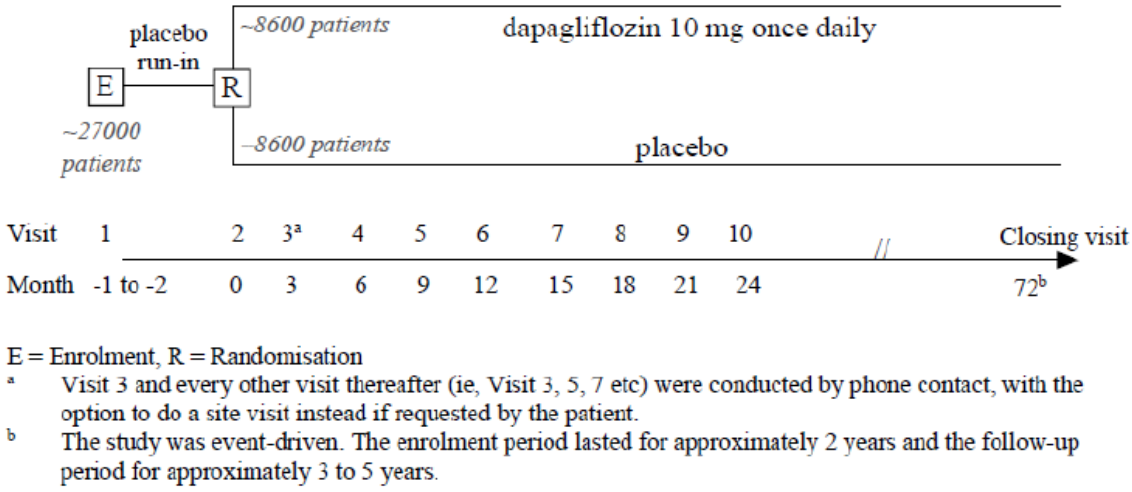
During a July 27, 2016 pre-IND meeting, the FDA agreed that, depending on the findings of the DAPA-CKD trial, it might be possible for the DECLARE trial to provide supportive evidence for a kidney-related claim.

Trial Design

Overview

The Dapagliflozin Effect on Cardiovascular Events (DECLARE) trial was conducted to fulfill a post-marketing requirement issued at the time the drug was approved for glycemic control, and the trial was designed to exclude a 30% increase in the risk of major adverse cardiovascular events (MACE). DECLARE was a multicenter, randomized (1:1), double-blind, placebo-controlled, event-driven study comparing dapagliflozin 10 mg to placebo on a background of standard of care therapy in adults with T2DM and established CV disease or at least two CV risk factors (Figure 10).

Figure 10 DECLARE Study Design



E = Enrolment, R = Randomisation

[a] Visit 3 and every other visit thereafter (ie, Visit 3, 5, 7 etc) were conducted by phone contact, with the option to do a site visit instead if requested by the patient.

[b] The study was event-driven. The enrolment period lasted for approximately 2 years and the follow-up period for approximately 3 to 5 years.

Source: DECLARE CSR, Figure 1

The kidney-related eligibility criteria are listed below. As Dr. Smith's consult notes, the eligibility criteria were not designed to identify patients with pre-existing diabetic nephropathy or chronic kidney disease and explicitly excluded patients with lower levels of kidney function.

Key pertinent or kidney-related inclusion criteria:

- Adult males or females ≥ 40 years of age
- Diagnosis of T2DM
- High risk for CV events defined as having either established CV disease and/or multiple risk factors[50]

Key kidney-related exclusion criteria

- CrCL<60 mL/min (based on the Cockcroft-Gault equation)

<u>Kidney-related study procedures</u>

Patients had phone assessments every 3 months and visited the study site every 6 months. Patients had central laboratory assessments at randomization, 6 months, 12 months, then annually, at the end of treatment, and at the end of study. This included measurement of serum creatinine, urinalysis including microscopy, and urine albumin-to-creatinine ratio (UACR).

Protocol amendment 5 specified that a repeat central laboratory serum creatinine measurement was to be obtained after at least 4 weeks if a patient was noted to have a

[50] Established CV disease was defined as either ischemic heart disease or cerebrovascular disease. Multiple risk factors were defined as either: No known CV disease and age≥ 55 in men and ≥ 60 years in women AND the presence of at least one of the following: dyslipidemia, hypertension or tobacco use. Details regarding inclusion/exclusion trial criteria are included in the original DECLARE review.

doubling of serum creatinine, serum creatinine >6 mg/dL, decrease in eGFR of ≥30% to an eGFR <60 mL/min/1.73 m^2, or an eGFR <15 mL/min/1.73 m^2.

Patients with a confirmed creatinine clearance below 30 mL/min were to discontinue study drug.

Investigational Drug Dosing:
Patients received visually identical tablets of either dapagliflozin 10 mg or placebo, which was to be taken orally, once daily in the morning and at approximately the same time each day.

Concomitant Medications:
During the trial, patients were to receive standard of care treatment for CV risk factors (hypertension, dyslipidemia, antithrombotic therapies) and be treated for T2DM to achieve glycemic goals as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). Adjustments to medications were at the Investigators' discretion. Unlike DAPA-CKD, DECLARE did not require that patients with diabetic nephropathy be taking a maximally tolerated dose of an ACEi or ARB.

Discontinuation of Investigational Product, Withdrawals, and Premature Trial Termination:
Patients were free to discontinue study drug use or to withdraw from the study at any time. Patients discontinuing study drug who did not withdraw consent for follow-up were to be assessed at each visit for AEs, CV events, body weight, and anti-diabetes medication. They were not required to complete laboratory assessments. Permanent discontinuation of study drug was permitted for patients meeting criteria for liver, kidney, or bladder cancer or due to pregnancy.

Study Endpoints

Primary endpoint
There were two primary endpoints; all components of the endpoints were adjudicated:

- Composite of CV death, myocardial infarction (MI), and ischemic stroke (MACE)
- Composite of hospitalization for heart failure and CV death

Secondary Endpoints:
There were two secondary endpoints:

- Composite of a confirmed sustained ≥40% decrease in eGFR to an eGFR <60 mL/min/1.73 m^2 (CKD-EPI),[51] ESKD (dialysis ≥90 days, kidney transplantation, a confirmed sustained eGFR <15 mL/min/1.73 m^2), and/or renal or CV death.
- All-cause mortality

[51] These events required confirmation of ≥ 40% reduction relative to baseline by 2 consecutive readings separated by ≥ 4 weeks. Time to onset would be the first of the two subsequent laboratory assessments. If no confirmation was obtained, the observation was not to be included in the main analysis.

All deaths were adjudicated. eGFR-based events were identified programmatically. Dialysis and kidney transplant events were reported by investigators and were not adjudicated. Baseline eGFR was defined as the last assessment on or before the date of randomization.

Pertinent Aspects of Statistical Analysis Plan

The SAP was revised several times based on feedback from the Agency. Of note, SAP edition 6.0 revised the statistical testing hierarchy to elevate the composite of heart failure hospitalization/CV death to a primary efficacy endpoint along with MACE. In addition, a renal composite endpoint was added to the closed testing procedure as a secondary endpoint. This revision was performed before the first of two formal interim analyses.

Interim analyses were conducted after a third and two-thirds of the planned total MACE events had accrued. According to the SAP, testing of the secondary endpoints was to occur hierarchically only if superiority was achieved on both primary endpoints.

The secondary kidney endpoint was analyzed using a Cox proportional hazards model with a factor for treatment group and stratified by CV risk category (CV risk factors/established CV disease) and baseline hematuria (yes/no).

The full analytic plan, including sample size calculations, analysis populations, handling of missing data, sensitivity analyses, and amendments, was reviewed in detail by the Agency with the original DECLARE NDA review.

7.1.4. DECLARE- Study Results

There were no concerns regarding compliance with good clinical practices or financial disclosures during the original DECLARE review.

Patient Disposition

In total, 17,160 patients were randomized 1:1 to dapagliflozin or placebo. Overall, 98.5% of randomized patients completed the trial, and vital status was known for over 99%. Treatment was prematurely discontinued by 21% and 25% of patients randomized to dapagliflozin and placebo, respectively (Table 17).

Table 17. DECLARE-Patient disposition

Disposition Event	Dapagliflozin 10mg n (%)	Placebo n (%)
Randomized	8582 (100.0)	8578 (100.0)
Completed trial	8473 (98.7)	8433 (98.3)
Discontinued from trial	109 (1.3)	145 (1.7)
Adverse event	0	0
Withdrawal of consent	97 (1.1)	127 (1.5)
Lost to follow-up	12 (0.1)	18 (0.2)
Discontinued treatment	1807 (21.1)	2144 (25.0)
Adverse event	671 (7.8)	548 (6.4)
Subject decision	825 (9.6)	1086 (12.7)
Study-specific discontinuation criteria	38 (0.4)	60 (0.7)
Liver enzyme elevation	6 (0.06)	8 (0.09)
Creatine clearance <30 mL/min	10 (0.1)	17 (0.2)
Bladder cancer	22 (0.3)	35 (0.4)
Pregnancy	0	0
Other Reason	273 (3.2)	450 (5.2)
Final Vital Status Available	8534 (99.4)	8514 (99.3)
Alive	8005 (93.3)	7944 (92.6)
Dead	529 (6.2)	570 (6.6)

Source: Derived from ADSL.xpt and ADDS.xpt datasets using JMP
Source: Original DECLARE clinical review, Table 5

According to the original DECLARE review, protocol deviations were randomly distributed between treatment arms, and there were no significant imbalances between treatment arms.

Demographic Characteristics

Table 18 shows key baseline characteristics for the DECLARE population, which were well-balanced. Over 90% of patients had an eGFR above 60 mL/min/1.73m^2 and a UACR below 300 mg/g. Approximately 8% of patients had a medical history of “nephropathy,” and 81% were taking an ACE inhibitor or ARB. As previously noted, the trial did was not designed to enroll patients with pre-existing chronic kidney disease and explicitly excluded patients with a creatinine clearance <60 mL/min.

Table 18. DECLARE – key baseline characteristics

	Dapagliflozin n [%] (N=8582)	Placebo n [%] (N=8578)
Age (mean [SD])	63.9 (6.8)	64 (6.8)
Male	5411 (63.1)	5327 (62.1)
Medical History		
Established CV disease	3474 (40.5)	3500 (40.8)
Hypertension	4686 (92.0)	4588 (90.6)
"Nephropathy"	714 (8.3)	691 (8.1)
ACE inhibitor or ARB	6974 (81.3)	6970 (81.3)
eGFR (mean [SD] mL/min/1.73m^2)	85.4 (15.8)	85.7 (16.0)
≥90	4137 (48.2)	4025 (46.9)
60-<90	3838 (44.7)	3894 (45.4)
<60	606 (7.1)	659 (7.7)
UACR (mg/g)		
<30	5819 (67.8)	5825 (67.9)
30-≤300	2017 (23.5)	2013 (23.5)
>300	594 (6.9)	575 (6.7)

Source: Applicant, Clinical Trial Report, Tables 10, 11, 12, and 11.1.4.2.1.
Source: Dr. Smith's consult dated October 15, 2019

Efficacy Results – Primary Endpoints

The incidence of MACE (CV death, myocardial infarction or ischemic stroke) was similar in the two treatment arms (8.8% and 9.4% for dapagliflozin and placebo, respectively). The estimated hazard ratio was 0.93 (95% CI 0.84, 1.03).

Dapagliflozin was superior to placebo for the reduction of the composite of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]). The treatment effect was driven by a reduction in the risk of hospitalization for heart failure (HR 0.73 [95% CI 0.61, 0.88]) with no change in the risk of CV death (Table 19).

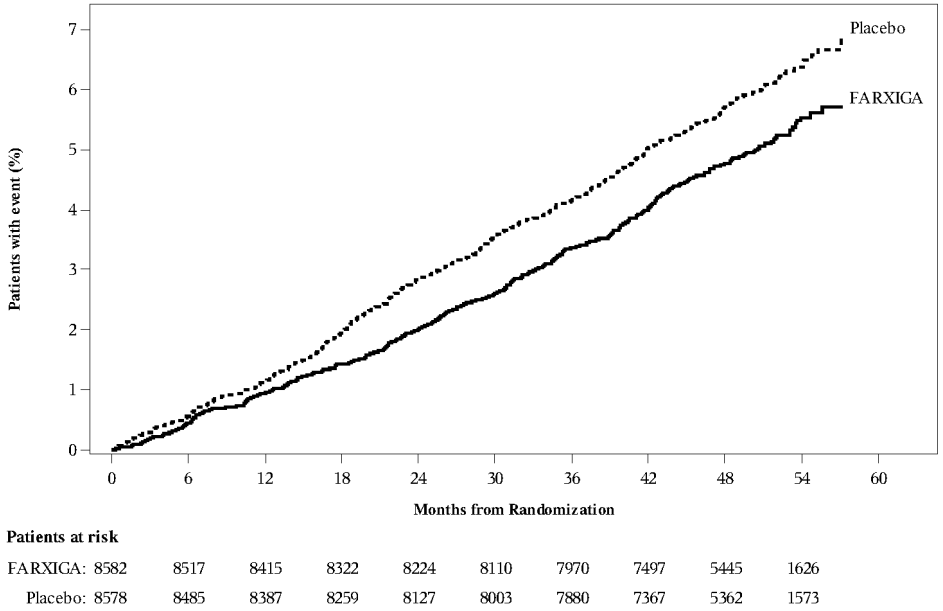
Based on these findings, on October 18, 2019, dapagliflozin was approved "to reduce the risk of hospitalization for heart failure in adults with T2DM and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors."

Table 19. Treatment Effects for the Primary Endpoints and Components in the DECLARE Study (Full Analysis Set)

	Patients with events n (%)		
Efficacy Variable (time-to-first occurrence)	**FARXIGA 10 mg N=8582**	**Placebo N=8578**	**Hazard ratio (95% CI)**
Primary Endpoints			
Composite of Hospitalization for Heart Failure, CV Death†	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)
Composite Endpoint of CV Death, MI, Ischemic Stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)
Components of the composite endpoints‡			
Hospitalization for Heart Failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)
CV Death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)
Myocardial Infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)
Ischemic Stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)

N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.
† p-value =0.005 versus placebo.
‡ total number of events presented for each component of the composite endpoints
Source: Farxiga PI, Section 14

Figure 4: Hospitalization for Heart Failure or CV Death in the DECLARE Study



Source: Farxiga PI, Section 14

Efficacy Results – Secondary Endpoint

Table 20 shows the results of the renal composite endpoint. Fewer patients in the dapagliflozin arm as compared to placebo experienced a composite endpoint event (HR 0.76 [95% CI 0.67, 0.87], nominal p-value <0.001); however, because the MACE endpoint did not reach statistical significance, there was no remaining alpha to test the secondary endpoints based on the pre-specified testing procedure. The results were therefore considered to be exploratory. Evaluation of the components of this endpoint revealed that the finding was primarily driven by differences in the number of patients experiencing a sustained ≥40% decrease in eGFR to <60 mL/min/1.73m^2. There were few ESKD or renal death events, but the number of such events numerically favored dapagliflozin as compared to placebo. The Kaplan-Meier curves separated around 18 months (Figure 11). The findings were generally consistent across subgroups of interest (see Table 59 in appendix).

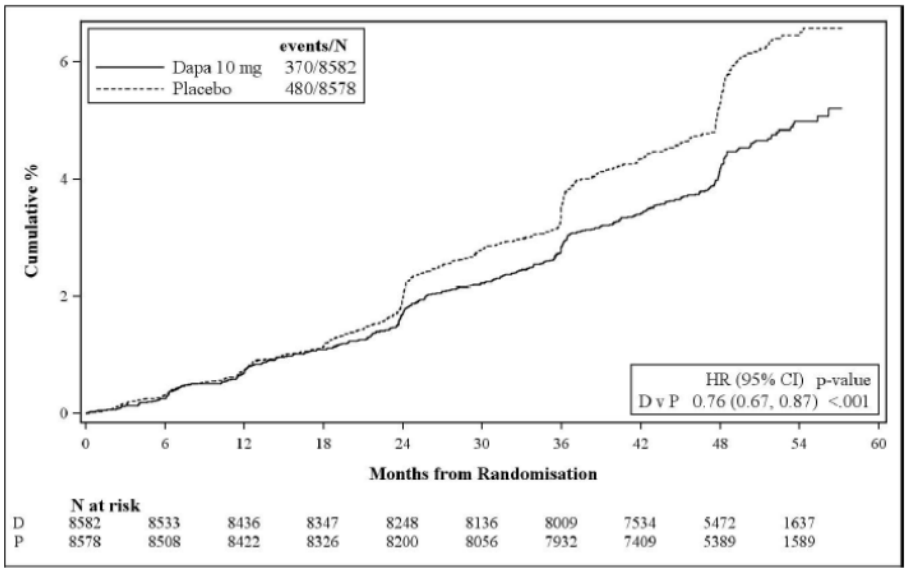
Table 20. DECLARE- Analysis of renal composite endpoint and components

	Dapagliflozin n [%] (N=8582)	**Placebo n [%] (N=8578)**	**HR (95% CI)**
Renal Composite	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87); nominal p-value <0.001
≥ 40% decrease in eGFR to an eGFR <60 mL/min/1.73 m^2	120 (1.4)	220 (2.6)	
ESRD	2 (<0.1)	11 (0.1)	
Renal or CV death	248 (2.9)	249 (2.9)	
Renal death	5 (<0.1)	7 (<0.1)	
CV death	243 (2.8)	242 (2.8)	
Individual Components (All Events)			
≥ 40% decrease in eGFR to an eGFR <60 mL/min/1.73 m^2	120 (1.4)	221 (2.6)	0.54 (0.43, 0.67)
ESRD	6 (<0.1)	19 (0.2)	0.31 (0.13, 0.79)
Renal or CV death	251 (2.9)	259 (3.0)	0.97 (0.81, 1.15)
Renal death	6 (<0.1)	10 (0.1)	0.60 (0.22, 1.65)
CV death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)

Source: Applicant, Clinical Trial Report, Table 20.

Source: Dr. Smith's consult, Table 2

Figure 11. DECLARE - Kaplan-Meier plot of time-to-first occurrence of renal composite event (FAS)



Source: DECLARE CSR, Figure 14.

During the DECLARE review, Dr. Smith raised several questions regarding the collection of renal endpoint events, which were conveyed in an Advice letter on December 18, 2019. With the current efficacy supplement, the Applicant provided responses related to the following issues:

1. *The FDA questioned how dialysis events were confirmed:*
   The Applicant stated that collection of dialysis events was not planned from the study start. During the trial, a member of the clinical study team monitored the blinded study database for all potential chronic dialysis events, including terms that could imply dialysis or kidney transplant. When potential events were identified, the team member requested that the investigator confirm a transplant or dialysis event had occurred as well as the duration of the event. Subsequently, a code for the event (i.e., DIALYSIS90) was entered in the database. The event start date was set to the corresponding adverse event onset date. Of the three dialysis events for which the FDA requested further information, one event (b) (6)) was not classified as chronic dialysis per the Applicant because the event had a duration of <90 days. The remaining two events, (b) (6) were confirmed as having a dialysis duration lasting >90 days by the Applicant by evaluation of other related SAEs (i.e., SAE for "end stage kidney disease" for (b) (6) and SAE for "shortness of breath" for event (b) (6).

   Reviewer's comment: The Applicant simply states that the "database was regularly searched for terms that could imply dialysis or renal transplant." Based on the Applicant's response it is not clear whether the "selected team member" in charge of monitoring for chronic dialysis events used a standardized algorithm to detect these events (i.e., use of SMQ) or whether the search terms were pre-specified. It also remains

unclear despite the additional clarification whether the chronic dialysis events met the definition of chronic dialysis (i.e., dialysis was ongoing for >90 days).

2. *The FDA questioned whether the ≥40% decline in eGFR to an eGFR*<60 mL/min/1.73m^2 *reflected irreversible loss of kidney function based on patient-level eGFR data:*

- Two cases (b) (6) were classified as meeting a 40% decline in eGFR to a value of <60 mL/min/1.73m^2 but later recovered. The Applicant noted that the eGFR trends around the time of the event for (b) (6) were likely related to dehydration that improved with treatment. The Applicant notes that the eGFR trends around the time of the event for (b) (6) were likely related to a change in heart failure medication. Although both events were flagged during a period of acute worsening of kidney function that improved to some degree, both subjects had a significant overall decline in eGFR decline from baseline during the trial that was consistent with the intent of the endpoint component.

- A third case ((b) (6)) had a spuriously elevated baseline value, and it was not clear that the patient had a meaningful decline in kidney function during the trial. The Applicant agreed with this assessment.

- A fourth case ((b) (6)) did not appear to meet criteria for a decline in eGFR by 40%. Per the Applicant, the patient met criteria for a 40% decline in eGFR based on the CKD-EPI equation (the equation used for efficacy analyses) but not the MDRD equation.

- The Applicant also reviewed all of the 341 events that met criteria of 40% decline in eGFR to a value of <60 mL/min/1.73 m^2 and identified 66 cases (25 cases of 120 total cases for dapagliflozin and 41 cases of 221 total cases for placebo) in which there was a potential reversal of the eGFR decline after the event was confirmed. We reviewed the individual eGFR trends for these 66 cases and noted that, in general, eGFR declined over time as compared to baseline, even in the cases where there were occasional transient increases in eGFR.

3. *FDA asked the Applicant to address the adequacy of eGFR follow-up over time and noted there was an apparent delay in obtaining repeat eGFR values.*

   DECLARE assessed kidney function at baseline, 6 months, 12 months and yearly thereafter. A central laboratory assessment was also required at the time of premature discontinuation of study drug. The Applicant notes that completeness of eGFR ascertainment declined from 100% at baseline to 68.9% at year 4 (the mean duration of the study). Approximately 23.1% of patients missing an eGFR measurement at the closing visit were patients who did not complete the study on treatment, and, therefore, were not required by protocol to have laboratory testing.

A member of the study team monitored trial data for potential eGFR declines. In addition, the trial had an automated system to alert investigators to an eGFR decline of ≥30%. Per the DECLARE protocol, the length of time between initial detection of an eGFR decline and a repeat value was specified as at least 4 weeks apart, but there was no upper limit. The Applicant reviewed all confirmed sustained eGFR events and noted that the median time from initial detection to confirmation was 169 days for dapagliflozin and 179 days for placebo. Reasons for delays in re-sampling included transfer to a different clinic and patient living far from study site.

Efficacy Results – Exploratory Renal Composite Endpoint Excluding CV death

To understand the kidney benefit, the Applicant also provided analyses of the an endpoint similar to the secondary renal composite endpoint but excluding CV death, which was a pre-specified exploratory endpoint (i.e., of time-to-first event of the composite of sustained ≥40% decrease in eGFR to an eGFR to <60 mL/min/1.73m^2, ESKD, and renal death); see Table 21. The findings of this analysis are consistent with the overall secondary renal endpoint; in brief, patients in the dapagliflozin are had fewer events as compared to placebo, and the findings were overwhelmingly driven by a sustained ≥40% decrease in eGFR.

Table 21 DECLARE – Time-to-first event of the composite of sustained ≥ 40% decrease in eGFR to <60 mL/min/1.73m^2, ESKD, and Renal Death (FAS)

Efficacy endpoints	Dapa 10 mg (N = 8582)		Placebo (N = 8578)			
	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	Hazard ratio (95% CI)	p-value[a]
Renal composite[b]	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43, 0.66)	< 0.001
Single components						
Sustained ≥ 40% decrease in eGFR[c]	120 (1.4)	3.5	221 (2.6)	6.5	0.54 (0.43, 0.67)	< 0.001
ESRD	6 (< 0.1)	0.2	19 (0.2)	0.6	0.31 (0.13, 0.79)	0.013
Renal death	6 (< 0.1)	0.2	10 (0.1)	0.3	0.60 (0.22, 1.65)	0.324

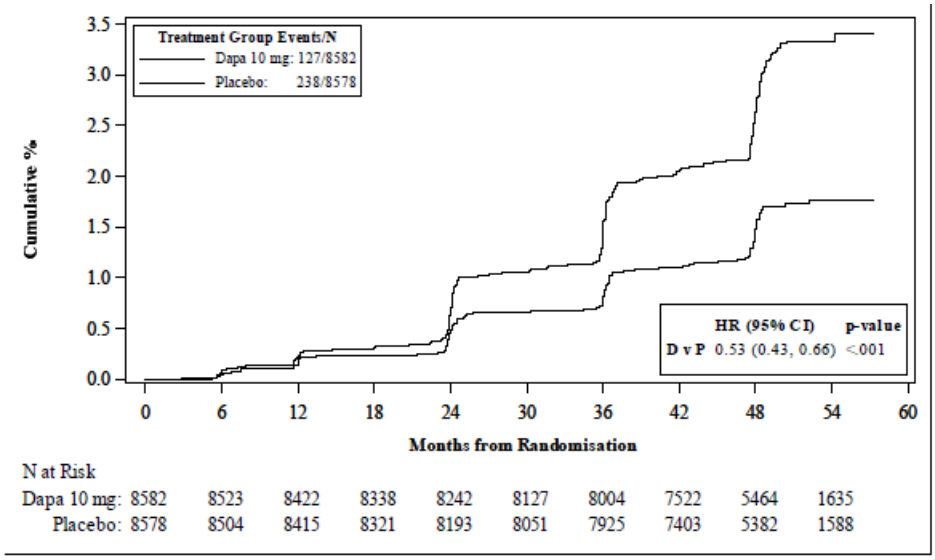
[a] All p-values are nominal.
[b] Renal composite endpoint defined as: sustained confirmed ≥ 40% decrease in eGFR to eGFR < 60 mL/min/1.73 m^2 using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m^2) and/or renal death as adjudicated by CEC.
[c] Time to onset would be the first of the 2 subsequent laboratory assessments

Event rate displayed as event rate per 1000 patient-years. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk group and haematuria with treatment as a model term.
CI, confidence interval; Dapa, dapagliflozin; ESRD, end-stage renal disease; FAS, full analysis set; N, number of patients per treatment group; n, number of patients with events; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CEC, Clinical Event Adjudication Committee.
Derived from: DECLARE CSR Tables 11.2.2.1.1 and 11.2.2.1.6.1 in the original DECLARE submission

Source: Summary of Clinical Efficacy, Table 7 DAPA-CKD submission.

As shown in Figure 12, the Kaplan-Meier curves separated around 12 months and continued to diverge during the trial.

Figure 12 DECLARE – Kaplan-Meier plot of the composite of sustained ≥ 40% decrease in eGFR, ESKD, and Renal Death (FAS)



N at risk is the number of patients at risk at the beginning of the period. Analysis of time from randomisation to first occurrence of event or censoring. Renal composite endpoint defined as sustained confirmed eGFR decrease ≥ 40% to eGFR < 60 mL/min/1.73 m^2 using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m^2) and renal death as adjudicated by Clinical Event Adjudication Committee.
1 month corresponds to 30 days. 2-sided p-value is displayed. P-value is nominal.
CI, confidence interval; Dapa, dapagliflozin; D, Dapa 10 mg; FAS, full analysis set; HR, hazard ratio; N, number of patients per treatment group; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; P, placebo; v, versus.
Source: Figure 7.5 in CTD Module 2.7.3 of the original DECLARE submission.

Source: Summary of Clinical Efficacy, Table 7 DAPA-CKD submission.

In subgroup analyses by eGFR and UACR category, there were nominal differences in events between treatment arms that favored dapagliflozin (Table 22). Although few patients had an eGFR<60 mL/min/1.73m^2 at enrollment, this subgroup had the largest number of events. The findings were similar for the subgroup with a UACR>300 mg/g.

Table 22 DECLARE - Time-to-first event of the composite of sustained ≥40% decrease in eGFR, ESKD and renal death by baseline eGFR and UACR (FAS)

	Dapagliflozin (N=8582)		Placebo (N=8578)		HR (95% CI)
	n	n [%]	n	n [%]	
eGFR					
≥90	4137	41 (1.0)	4025	79 (2.0)	0.50 (0.34, 0.73)
60-<90	3838	65 (1.7)	3894	121 (3.1)	0.54 (0.40, 0.73)
<60	606	21 (3.5)	659	38 (5.8)	0.60 (0.35, 1.02)
UACR (mg/g)					
<30	5819	50 (0.9)	5825	95 (1.6)	0.52 (0.37, 0.74)
30-≤300	2017	39 (1.9)	2013	66 (3.3)	0.59 (0.39, 0.87)
>300	594	31 (5.2)	575	75 (13.0)	0.38 (0.25, 0.58)

Source: Applicant, Clinical Trial Report, Tables 11.2.2.1.2 and 11.2.2.1.6.3.

Source: Dr. Smith's consult, Table 3

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7.1.5. Assessment of Efficacy Across Trials

Section is not applicable.

7.1.6. Integrated Assessment of Effectiveness

In support of additional efficacy claims for dapagliflozin, the Applicant provided the results of two phase 3 studies, DAPA-CKD and DECLARE (a trial that was previously reviewed by the FDA).

DAPA-CKD was a randomized, double-blind, placebo-controlled outcomes trial in which 4,304 patients with an eGFR ≥25 and ≤75 mL/min/1.73m^2 and UACR ≥200 and ≤5000 mg/g on a maximally tolerated ACEi or ARB were randomized equally to 10 mg of dapagliflozin or placebo.

DAPA-CKD was stopped early due to findings of overwhelming efficacy during an unplanned assessment by the trial's DMC. The DMC's decision to recommend early trial termination was informed by the published literature in the setting of strong efficacy findings for DAPA-CKD and no new safety findings.

Indication in Patients with CKD
The primary efficacy findings from the DAPA-CKD trial showed that dapagliflozin reduced the risk of the primary composite endpoint: ≥50% sustained decline in eGFR, ESKD (including sustained eGFR <15 mL/min/1.73m^2, chronic dialysis, or receiving a kidney transplant), and CV death or renal death. After a median follow-up of 28.5 months, a total of 197 (9.2%) patients randomized to dapagliflozin and 312 (14.5%) patients randomized to placebo had a primary efficacy event. The estimated adjusted hazard ratio comparing dapagliflozin and placebo was 0.61 (95% CI 0.51-0.72; p<0.0001). The primary efficacy findings were driven primarily by a sustained ≥50% eGFR decline and ESKD; there were too few patients to draw conclusions regarding renal death (eight patients total in the trial). Approximately 20% of patients were censored early because of missing eGFR assessments; however, the trial's findings were robust to sensitivity analyses using alternative missing data assumptions. Subgroup analyses based on key demographic subgroups, baseline disease characteristics, and etiology of CKD were consistent with the primary efficacy findings.

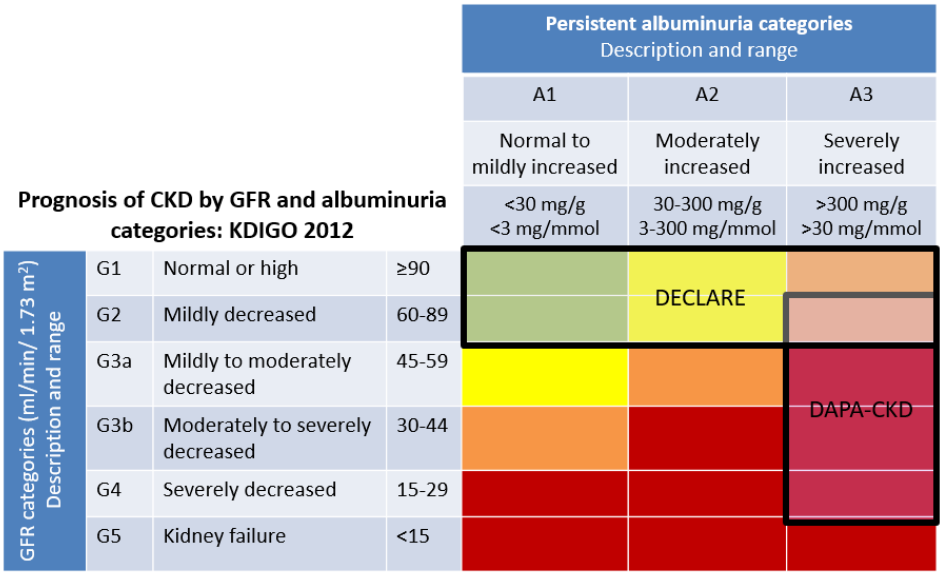
The efficacy findings from the DECLARE trial (NDA 202293, supplement 18) are supportive of a kidney benefit in patients with T2DM. The DECLARE trial was a multicenter, randomized, double-blind, placebo-controlled, event-driven, CV outcomes trial. Based on the study's results, on October 18, 2019, dapagliflozin was labeled for an indication to reduce the risk of hospitalization for heart failure in adults with T2DM and established CV disease or multiple CV risk factors. The secondary renal endpoint was a composite of a confirmed sustained ≥40% decrease in eGFR to an eGFR <60 mL/min/1.73 m^2, ESKD (dialysis ≥90 days, kidney transplant, or a confirmed sustained eGFR <15 mL/min/1.73 m^2), renal or CV death. Fewer patients in the

dapagliflozin arm as compared to placebo experienced a renal composite endpoint event (HR 0.76 [95% CI 0.67, 0.87], nominal p-value <0.001); the findings were mainly driven by declines in eGFR.

(b) (4)

When taken together, as shown in Figure 13, the results from DAPA-CKD and DECLARE provide evidence of effectiveness for dapagliflozin across a breadth of severity of chronic kidney disease. In addition, DAPA-CKD enrolled patients with a variety of etiologies of CKD (the trial mainly excluded patients with autosomal dominant or autosomal recessive polycystic kidney disease or patients with recent history of immunosuppressive therapy for the treatment of kidney disease), most commonly diabetic nephropathy (59%), ischemic/hypertensive nephropathy (16%), and chronic glomerulonephritis (16%). The remaining 10% of patients had a broad representation of other etiologies of CKD.

Figure 13: Populations of Chronic Kidney Disease Severity Evaluated in DAPA-CKD and DECLARE



Source: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

(b) (4)

(b) (4)

Secondary Endpoints in DAPA-CKD

As noted in Section 7.1.2, there was no pre-specified approach to testing the secondary endpoints after an unplanned interim analysis led to early termination of the trial; however, we note the following regarding the key secondary endpoints:

- The first secondary endpoint was a renal composite endpoint that included all components of the primary endpoint except for CV death. The findings were consistent with the primary endpoint results and considered statistically robust (HR of 0.56 [95% CI: 0.45; 0.68; p<0.0001]). We believe it is reasonable to describe the findings in labeling.
- The second secondary endpoint was a composite of CV death and hospitalization for heart failure. Aside from the issue of specification of alpha for testing the secondary endpoints, the findings were strong (HR: 0.71 [95% CI: 0.55, 0.92; p=0.0089]), and there are also data from other large trials (i.e., DAPA-HF and DECLARE) that support a benefit of dapagliflozin on heart failure hospitalizations. We therefore believe it is reasonable to grant a claim based on heart failure hospitalizations for patients with CKD.
- The third secondary endpoint was all cause mortality. Aside from the issue of specification of alpha for testing the secondary endpoints, the findings were strong (HR: 0.69 [95% CI: 0.53, 0.88; p=0.0035]) despite the limited long-term follow-up. The mortality findings appeared to be driven by effects on CV causes of death, for which they will get an indication based on other endpoints, but also non-CV causes of death, including infections and malignancies, via unclear mechanism. We believe it is reasonable to describe the results of this endpoint in the clinical studies section of the label given the importance of this information to patients and providers; (b) (4)

7.2. Review of Safety

7.2.1. Safety Review Approach

The safety of dapagliflozin has been well studied in thousands of patients with T2DM and HF. The safety review of dapagliflozin in patients with CKD focused on previously identified risks of SGLT2 inhibitors and included a review of data quality,[53] adverse event (AE), laboratory

[53] Data quality was examined using JumpStart Service -Data Fitness Analysis.

data, and vital sign data collected in the pivotal trial, DAPA-CKD. In addition to the DAPA-CKD clinical study report (CSR), the documents shown in the table below were reviewed.

Table 25. Documents Reviewed

Document	Period Covered or Submission Date	Report Date
FDA DMEP Clinical review of efficacy supplement 18 – dapagliflozin for T2DM patients with established cardiovascular disease (cardiovascular outcome trials, DECLARE)	Submission date 12/18/2018	9/16/2019
FDA DCN Clinical review of efficacy supplement 20- dapagliflozin for HFrEF patients (DAPA-HF)	Submission date 11/6/2019	4/23/2020

Reviewer's Table

Safety analyses were performed on the treated population (received at least one dose of study drug) and are primarily presented in this review for the on-treatment period. For adverse events of special interest (AESIs) such as fractures and amputations, the on- and off-treatment period was used. Definitions of data periods for analyses are shown in Table 26.

Table 26. Definitions and Data Periods for Safety Analyses

Analysis Set	Analysis Population	Dapagliflozin Patients	Placebo Patients	Data Period
On-treatment	Treated patients	2149	2149	Between first dose of treatment and 30 days after last dose of treatment
On- and Off-treatment	Treated patients	2149	2149	After first dose of study drug regardless whether patients were on or off study treatment at the time of event

Reviewer's Table

SAS version 9.4 and the Office of Computational Science table builder tool were used for most analyses; MedDRA Adverse Event Diagnosis (MAED) and JMP Clinical were also used. Results are presented as percent of patients (%) and rate per 100 patient-years

7.2.2. Review of the Safety Database

Overall Exposure

In total, there were 4,448 patient-years of exposure to dapagliflozin in the study. The median duration of dapagliflozin exposure in DAPA-CKD was 27 months (or 1.5 years). See Table 27 for additional information on duration of treatment in DAPA-CKD.

Table 27. Duration of Exposure, Safety Population, DAPA-CKD

Parameter	Dapa 10 mg N=2149	Placebo N=2149
Duration of treatment (months)		
Mean (SD)	24.8 (9.4)	24.3 (9.6)
Median (Min, Max)	27.3 (0.03, 39.0)	27.0 (0.03, 38.8)
Patients treated, by duration, n (%)		
Any duration (at least one dose)	2149 (100)	2149 (100)
<1 month	28 (1.3)	29 (1.4)
≥1 month	2121 (98.7)	2120 (98.7)
≥6 months	1946 (90.6)	1932 (89.9)
≥12 months	1865 (86.8)	1829 (85.1)
≥18 months	1773 (82.5)	1745 (81.2)
≥24 months	1423 (66.2)	1364 (63.5)
≥28 months	992 (46.2)	945 (44.0)
≥32 months	445 (20.7)	411 (19.1)
≥36 months	80 (3.7)	70 (3.3)

Reviewer's table; Source: adsl & adex

Adequacy of the safety database:

The duration of exposure in DAPA-CKD, in combination with the extensive prior clinical experience, is considered adequate to characterize the safety of dapagliflozin in patients with CKD.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The JumpStart Service was consulted to review data quality for this NDA, including an SDTM assessment and SDTM to ADaM traceability. The overall data and submission quality are reasonable. AE coding was evaluated using the JumpStart output in which a matching score was calculated comparing the verbatim term to the coded preferred term (PT). The AE coding was reasonable overall.

Categorization of Adverse Events

Adverse events in DAPA-CKD were only to be recorded if they were SAEs; if the AE was the reason for permanent discontinuation from study drug, study drug interruption, or dose reduction; or if the AE qualified as an AESI. Adverse events were primarily analyzed by Medical Dictionary for Regulatory Activities (MedDRA; Version 23.0) preferred term and by pooling AEs with a similar medical concept (referred to as the MedDRA SMQ or FDA MedDRA Query [FMQ]). The FMQ analysis is similar to a customized MedDRA query. Adverse events of special interest for dapagliflozin included AEs suggestive of volume depletion, renal AEs, diabetic ketoacidosis (DKA), major hypoglycemic events, fractures, AEs leading to amputation (AEs that indicate an amputation), and AEs leading to a risk of lower limb amputation (AEs that might

precede an amputation). For AESIs, the Applicant either used a MedDRA SMQ or grouped a pre-defined list of preferred terms, similar to a customized MedDRA query. The list of PTs for each AESI can be found here. In addition, all potential DKA events were adjudicated by an independent DKA Adjudication Committee.

Routine Clinical Tests

The schedule and type of laboratory assessments in DAPA-CKD can be found here. Central laboratory variables were measured at all study visits, including hematocrit, urine albumin, urine creatinine, blood urea nitrogen (BUN), creatinine, HbA1c, potassium, and sodium. Other laboratory variables were measured at planned visits. Per protocol, unscheduled laboratory samples were to be sent to the central laboratory for analysis. Overall, the safety assessments in DAPA-CKD were acceptable.

7.2.4. Safety Results

Deaths

As discussed under efficacy, all-cause mortality was lower in the dapagliflozin as compared to the placebo group (Table 15). Adverse events that led to death during the whole study period (i.e., on- and off-treatment) based on the AE case report forms are shown in Table 28. The placebo group had a slightly higher incidence of death due to cardiac failure, infections and malignancy compared to the dapagliflozin group. These findings are generally consistent with the adjudicated causes of death shown in Table 16 above.

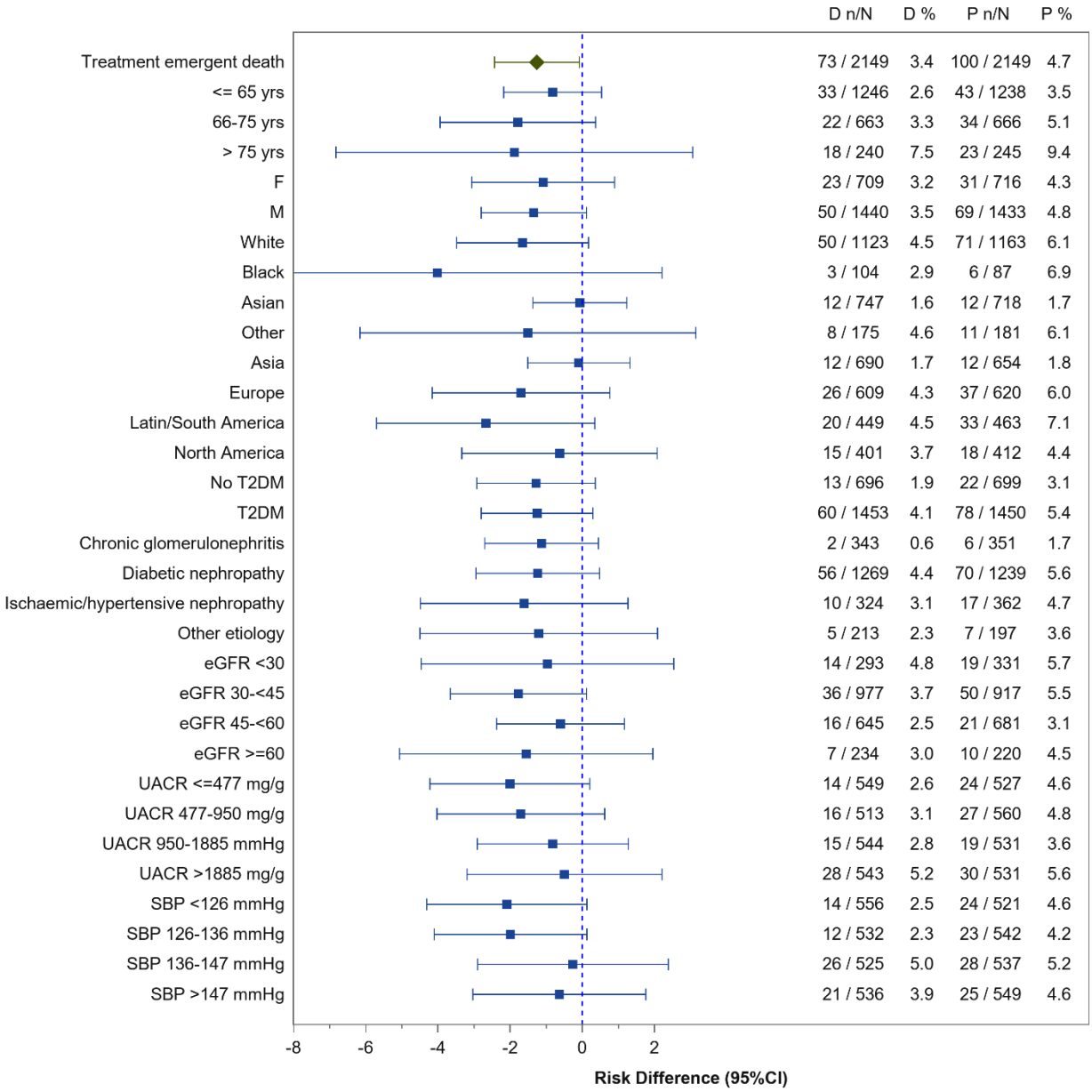
Table 28. Death in Safety Population, Dapa-CKD, On- and Off-Treatment[1]

	Dapa 10mg (N=2149)	Placebo (N=2149)
Total AE with fatal outcome	**106 (4.9)**	**159 (7.4)**
Treatment emergent death	**73 (3.4)**	**100 (4.7)**
Cardiac disorders (SOC)	27 (1.3)	27 (1.3)
Myocardial infarction[2]	12 (0.6)	8 (0.4)
Cardiac failure[3]	5 (0.2)	11 (0.5)
General disorders and administration site conditions (SOC)	12 (0.6)	13 (0.6)
Death/Sudden death/Sudden cardiac death	10 (0.5)	13 (0.6)
Infections and infestations (SOC)	11 (0.5)	20 (0.9)
Pneumonia/pneumonia bacterial	4 (0.2)	8 (0.4)
Septic shock/sepsis[4]	6 (0.3)	10 (0.5)
Neoplasms benign, malignant and unspecified (SOC)	8 (0.4)	13 (0.6)
Non-treatment emergent deaths	33 (1.5)	59 (2.7)
Death/sudden death/sudden cardiac death/cardiac death	10 (0.5)	18 (0.8)
Cardiac disorders (SOC)	7 (0.3)	14 (0.7)
Myocardial infarction[2]	1 (0.0)	6 (0.3)
Infections and infestations (SOC)	4 (0.2)	11 (0.5)
Septic shock/sepsis[4]	3 (0.1)	7 (0.3)

Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool
1.This table only includes SOC with a frequency of greater than N ≥ 10 in either group and only lists preferred term with a frequency of N ≥ 5 in either group.
2. Myocardial infarction includes acute myocardial infarction and myocardial infarction
3. Cardiac failure includes cardiac failure, cardiac failure acute, acute left ventricular failure, cardiac failure chronic, cardiac failure congestive, cardiopulmonary failure and cardiogenic shock
4. Septic shock/sepsis includes septic shock, device related sepsis, sepsis, pulmonary sepsis and staphylococcal sepsis
Abbreviation: SOC, system organ class, N, number of subjects in group

Subgroup analyses for treatment emergent deaths were performed based on age, gender, race, region, diabetes status at baseline, etiology of CKD (diabetic nephropathy, chronic glomerulonephritis, ischemic/hypertensive neurology, other), eGFR at baseline (<30, 30-<45, 45-<60, ≥60 mL/min/1.73m^2), UACR at baseline (quartile), and SBP at baseline (quartile). Overall, the death results were consistent across subgroups with a risk difference (RD) <1 for all categories (Figure 14).

Figure 14. Treatment Emergent Death by Subgroup, Safety Population, DAPA-CKD



Source: Reviewer's analysis, dataset: adsl & adae
Abbreviation: T2DM, type 2 diabetes mellitus, eGFR, estimated glomerular filtration rate, UACR, urine albumin-to-creatinine ratio SBP, systolic blood pressure, D, dapagliflozin, P, placebo, n, number of event, N, number of subjects in each group

Serious Adverse Events

The overall incidence of SAEs was lower in the dapagliflozin group compared with the placebo group: 594/2149 (27.6%) and 674/2149 (31.4%), respectively. There were no preferred terms that occurred with a frequency of at least 0.5% greater in the dapagliflozin group compared to the placebo group. Table 29 summarizes actions taken in response to an SAE and the outcomes of SAEs and shows the most common reported SAEs (i.e., grouped preferred terms that capture a similar medical concept using MedDRA SMQ and FMQ and occurring in at least 2% in either group). The incidence of more frequently reported SAEs was generally lower in patients treated with dapagliflozin than placebo.

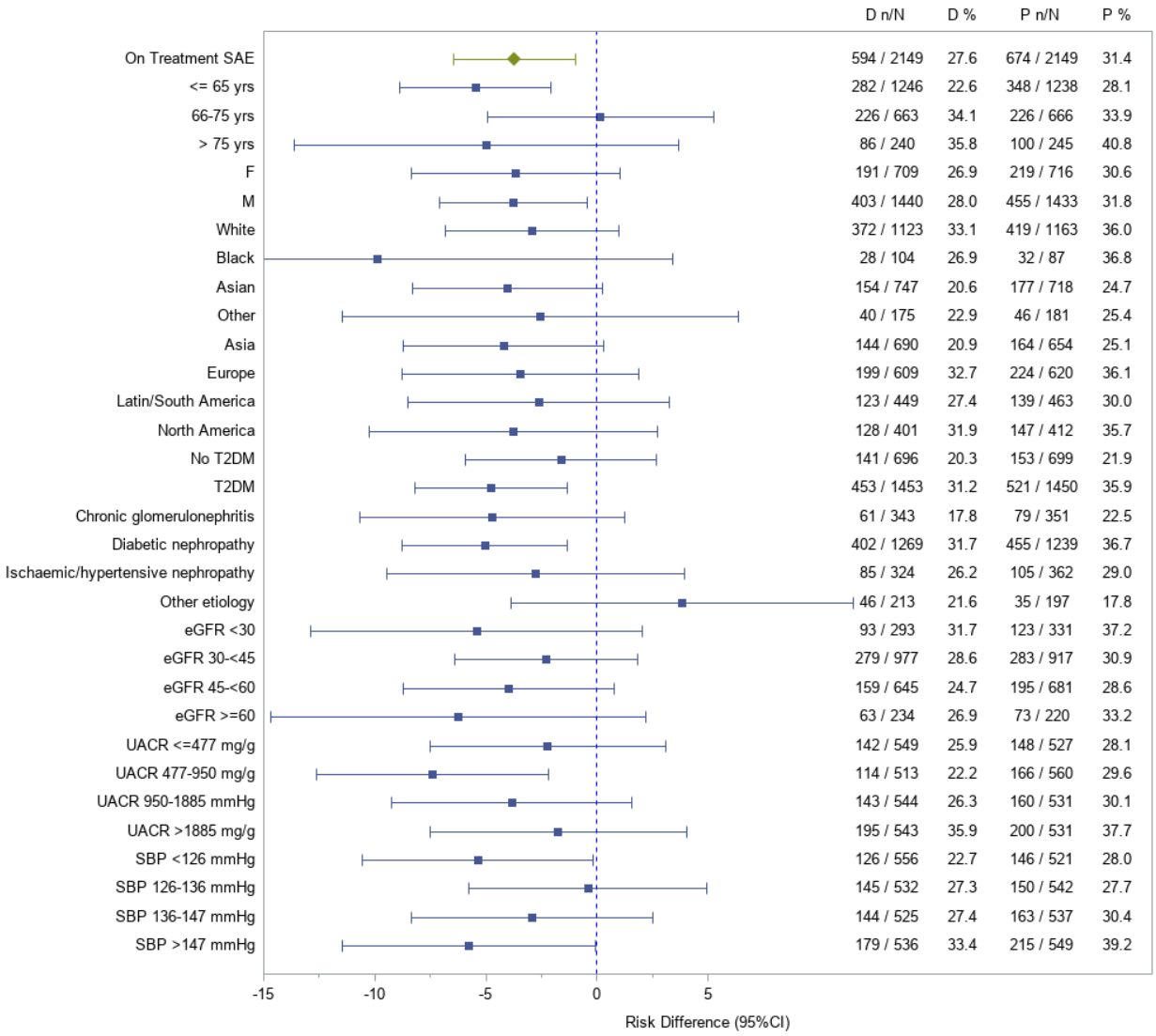
Table 29. Serious Adverse Events, Safety Population, DAPA-CKD, On-Treatment

Treatment-Emergent Serious Adverse Event	Dapa 10mg (N=2149)	Placebo (N=2149)
Any SAE	594 (27.6)	674 (31.4)
DOSE NOT CHANGED	396 (18.4)	445 (20.7)
DRUG INTERRUPTED	188 (8.7)	187 (8.7)
DRUG WITHDRAWN	63 (2.9)	71 (3.3)
RECOVERED/RESOLVED	459 (21.4)	511 (23.8)
NOT RECOVERED/NOT RESOLVED	77 (3.6)	101 (4.7)
RECOVERED/RESOLVED WITH SEQUELAE	77 (3.6)	75 (3.5)
FATAL	73 (3.4)	100 (4.7)
RECOVERING/RESOLVING	36 (1.7)	50 (2.3)
SAE in at least 2% of patients		
Cardiac failure (SMQ, narrow)	58 (2.7)	88 (4.1)
Myocardial ischemia (FMQ, narrow)	59 (2.8)	77 (3.6)
Ischemic central nervous system vascular conditions (SMQ, narrow)	60 (2.8)	52 (2.4)
Pneumonia (FMQ, narrow)	42 (2.0)	65 (3.0)
Malignancy (FMQ, narrow)	45 (2.1)	52 (2.4)
Acute kidney injury (FMQ, narrow)	39 (1.8)	52 (2.4)

Source: Reviewer's table, dataset: adsl & adae, MAED, OCS Analysis Studio-Custom Table Tool

Subgroup analyses for treatment emergent SAEs were performed based on age, gender, race, region, diabetes status at baseline, etiology of CKD (diabetic nephropathy, chronic glomerulonephritis, ischemic/hypertensive neurology, other), eGFR at baseline (<30, 30-<45, 45-<60, ≥60 mL/min/1.73m^2), UACR at baseline (quartile), and SBP at baseline (quartile). Overall, the SAE results were consistent across subgroups with a RD <1 for most categories. There was a higher incidence of SAEs in the dapagliflozin group compared to the placebo group among patients with an etiology of CKD grouped as "other." It should be noted that this is a small subgroup of varied CKD etiologies. Further investigation of the types of SAEs in this subset did not raise a specific safety concern. There was no cluster of similar events, and no preferred term was reported by more than two patients in the dapagliflozin group. The majority of these SAEs (≥ 80%) resolved in both groups.

Figure 15. On Treatment SAE by Subgroup, Safety Population, DAPA-CKD

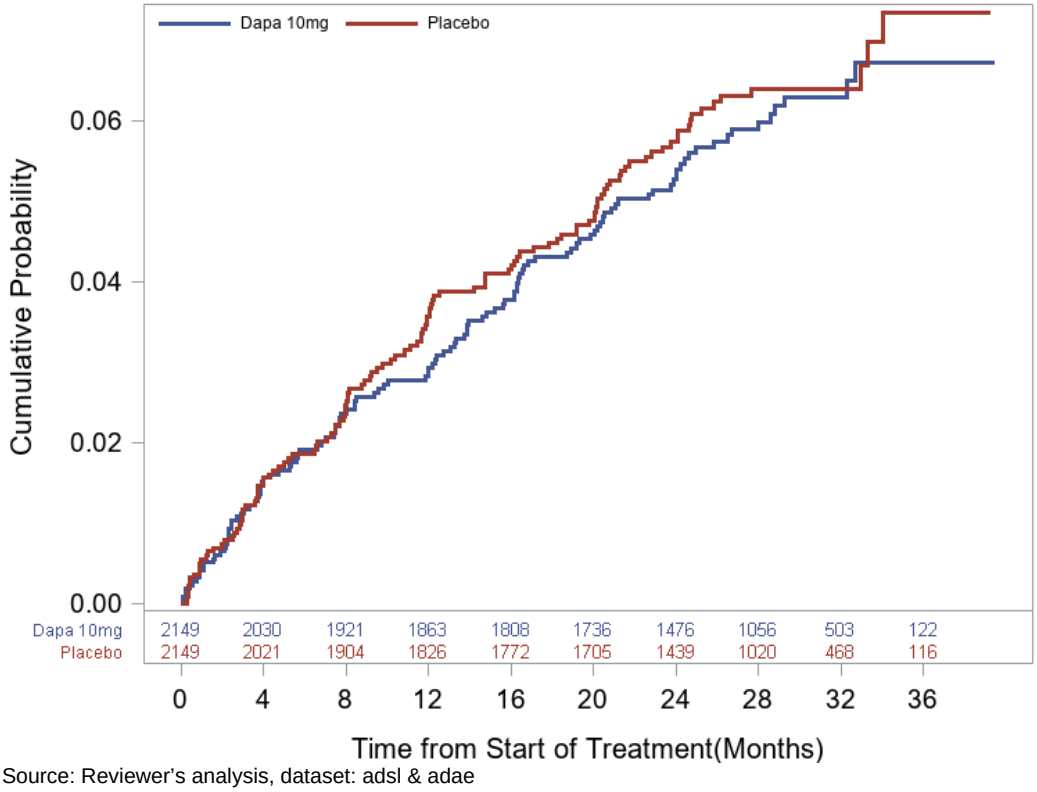


Source: Reviewer's analysis, dataset: adsl & adae
Abbreviation: T2DM, type 2 diabetes mellitus, eGFR, estimated glomerular filtration rate, UACR, urine albumin-to-creatinine ratio SBP, systolic blood pressure, D, dapagliflozin, P, placebo, n, number of event, N, number of subjects in each group

Dropouts and/or Discontinuations Due to Adverse Effects

The incidence of treatment discontinuations due to an AE was similar between the two groups throughout the study (Figure 16). Approximately 5-6% of patients in both arms discontinued study drug due to an AE. The most common reasons for discontinuation in both groups were acute or chronic renal failure; the percentage of patients with discontinuations for such events was similar in the two arms. There were 7 (0.3%) patients with an AE leading to discontinuation related to a urinary tract infection in the dapagliflozin group and 3 (0.1%) in the placebo group.

Figure 16: Kaplan-Meier Plot of the Cumulative Percentage of Subjects with Permanent Discontinuation of Study Drug Due to An Adverse Event



Source: Reviewer's analysis, dataset: adsl & adae

Table 30. Adverse Events Leading to Discontinuation, Safety Population, DAPA-CKD

	Dapa 10mg (N=2149)	Placebo (N=2149)
DRUG WITHDRAWN	118 (5.5)	123 (5.7)
Acute renal failure (SMQ)	27 (1.3)	31 (1.4)
Glomerular filtration rate decreased	9 (0.4)	10 (0.5)
Renal impairment	9 (0.4)	12 (0.6)
Acute kidney injury	5 (0.2)	6 (0.3)
Blood creatinine increased	2 (0.1)	1 (0.0)
Renal failure	2 (0.1)	2 (0.1)
Chronic kidney disease/end stage kidney disease	17 (0.8)	13 (0.6)
Ischemic central nervous system vascular conditions (SMQ)	6 (0.3)	5 (0.2)
Urinary tract infections	7 (0.3)	3 (0.1)

Source: Reviewer's table, dataset: adsl & adae, MAED, OCS Analysis Studio-Custom Table Tool

Adverse Events of Special Interest

For non-serious AEs, only AESIs and AEs leading to discontinuation or dose reduction were reported. Adverse events of special interest are summarized in Table 31. Overall, the incidence of these events was similar between the two arms, although volume depletion events were slightly higher in the dapagliflozin arm compared with placebo. For AESIs occurring in at least 5% of treated patients (volume depletion, renal events, and AEs leading to a risk for lower limb amputation), subgroup analyses were performed.

Adverse Event of Special Interest	Dapa 10mg (N=2149)		Placebo (N=2149)	
	AE	SAE	AE	SAE
Symptoms of volume depletion	120 (5.6)	16 (0.7)	84 (3.9)	15 (0.7)
Renal event	144 (6.7)	54 (2.5)	169 (7.9)	69 (3.2)
Major hypoglycemic event	14 (0.7)	6 (0.3)	28 (1.3)	14 (0.7)
Fracture[1]	85 (4.0)	40 (1.9)	69 (3.2)	28 (1.3)
Definite or Probable DKA[2]	0	0	2 (0.1)	2 (0.1)
Amputation[1]	36 (1.7)	34 (1.6)	39 (1.8)	38 (1.8)
AEs leading to a risk for lower limb amputation[1]	220 (10.2)	76 (3.5)	200 (9.3)	83 (3.9)

Table 31. Incidence of Adverse Events of Special Interest, Safety Population, DAPA-CKD

1. Adverse events were analyzed for both on- and off-treatment
2. There were 22 patients in the dapagliflozin arm and 20 patients in the placebo arm had a potential DKA event that was sent for adjudication.

Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

AEs Suggestive of Volume Depletion

The incidence of AEs suggestive of volume depletion was 5.6% in the dapagliflozin group and 3.9% in the placebo group, corresponding to event rates of 2.7 and 1.9 per 100 patient-years, respectively. The most commonly reported AE related to volume depletion in both groups was hypotension (Table 32). The incidence of SAEs of symptoms of volume depletion was similar between two treatment groups (Table 31). There were no fatal cases in either arm. Most events (>90%) in the dapagliflozin group resolved and did not require any changes in dapagliflozin dosing (71%).

Subgroup analyses for AEs suggestive of volume depletion were performed including age, gender, race, region, diabetes status at baseline, etiology of CKD (diabetic nephropathy, chronic glomerulonephritis, ischemic/hypertensive neurology, other), eGFR at baseline (<30, 30-<45, 45-<60, ≥60 mL/min/1.73m^2), UACR at baseline (quartile) and SBP at baseline (quartile) (Figure 17.). In general, the results were consistent across most of subgroups with a RD close to the overall point estimate of 1.7. Older patients (>75 years), other race, patients in North America, and patients with the CKD etiology "other" had a slightly higher incidence compared to those in

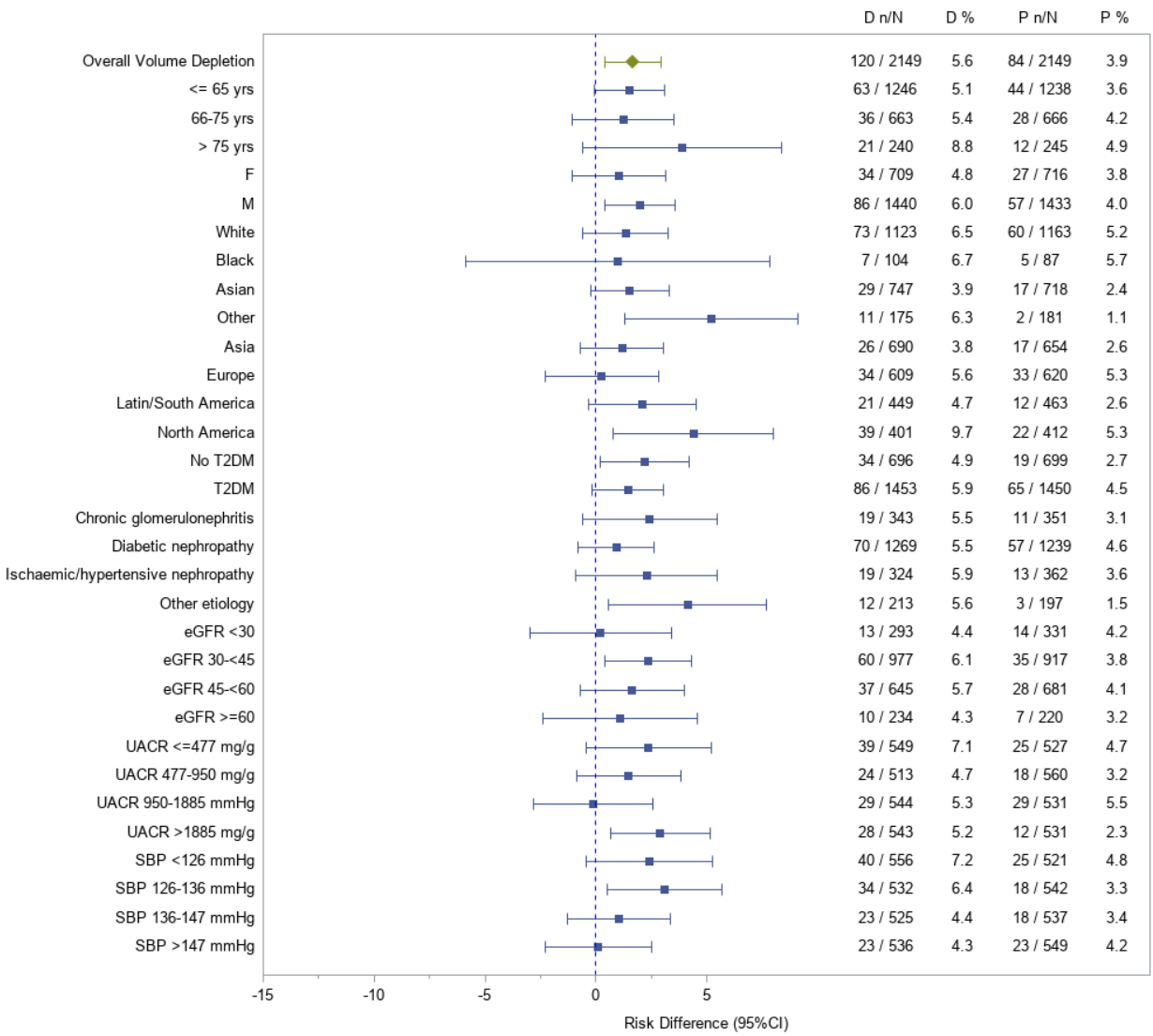
the placebo group; however, the overall point estimate was included in the 95% CIs of these subgroups.

Table 32. Incidence of Adverse Events Suggestive of Volume Depletion by Preferred Terms, Safety Population, DAPA-CKD, On-Treatment Period

	Dapa 10mg (N=2149)	Placebo (N=2149)
VOLUME DEPLETION	120 (5.6)	84 (3.9)
Hypotension	47 (2.2)	28 (1.3)
Hypovolemia	37 (1.7)	21 (1.0)
Dehydration	17 (0.8)	12 (0.6)
Syncope	12 (0.6)	10 (0.5)
Orthostatic hypotension	11 (0.5)	10 (0.5)
Blood pressure decreased	2 (0.1)	3 (0.1)
Hypovolemic shock	1 (0.0)	0
Urine flow decreased	1 (0.0)	0
Urine output decreased	1 (0.0)	0

Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

Figure 17. Volume Depletion AEs by Subgroup, Safety Population, DAPA-CKD, On-Treatment Period



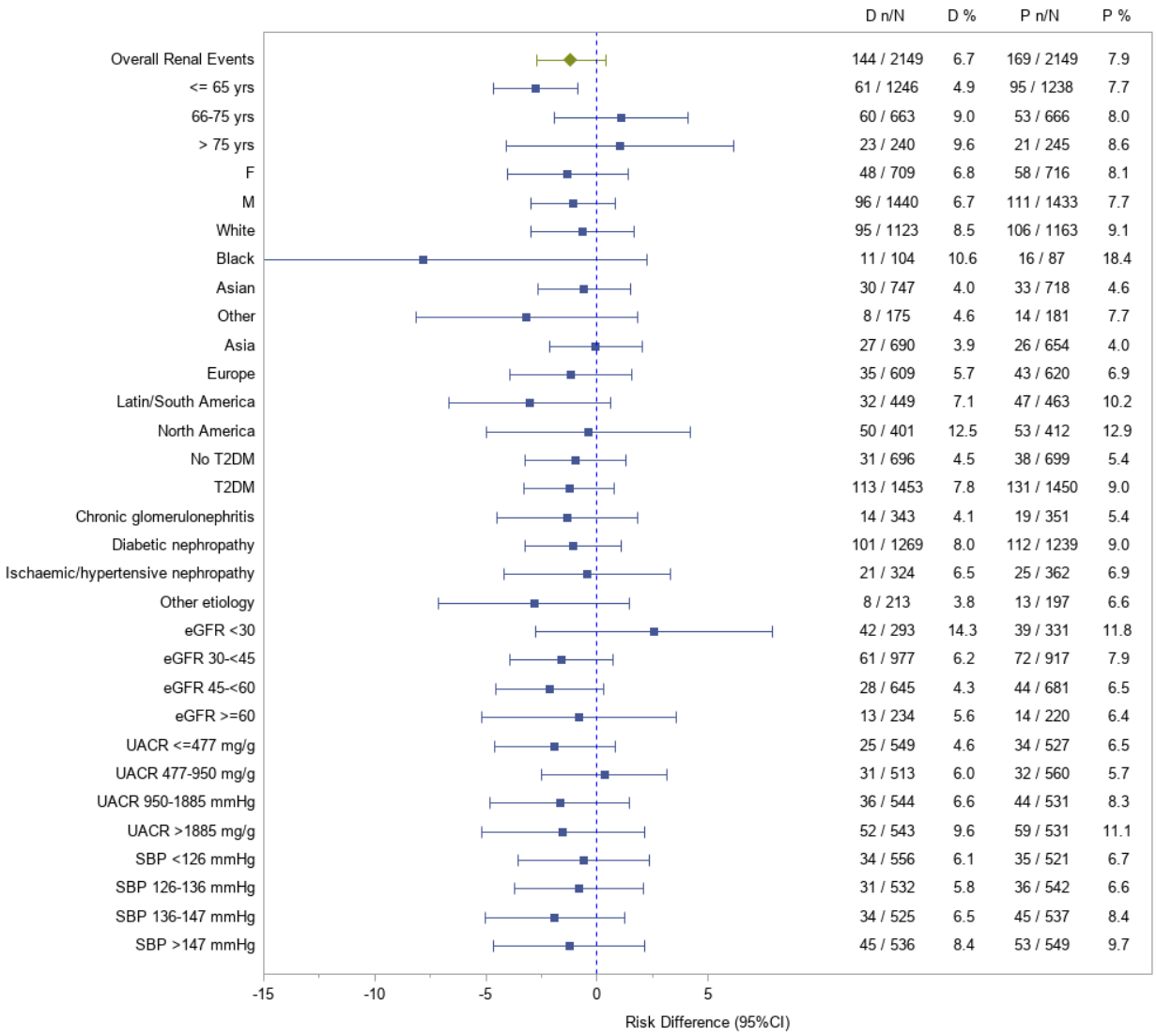
Source: Reviewer's analysis, dataset: adsl & adae
Abbreviation: T2DM, type 2 diabetes mellitus, eGFR, estimated glomerular filtration rate, UACR, urine albumin-to-creatinine ratio SBP, systolic blood pressure, D, dapagliflozin, P, placebo, n, number of event, N, number of subject in each group

Renal Adverse Events

The Applicant evaluated renal AEs using the MedDRA SMQ "acute renal failure." The incidence of renal AEs was similar between the treatment arms: 6.7% in the dapagliflozin arm and 7.9% in the placebo arm, corresponding to event rate of 4.2 and 4.8 per 100 patient-years, respectively. The results were also similar between the treatment arms for the incidence of SAEs (Table 31) and DAEs (Table 30). Evaluation of renal adverse events using the FMQ for "acute kidney injury" yields similar results (Appendix 12.10 Table 60). There were two fatal cases in the dapagliflozin arm and one fatal case in the placebo arm. Both fatal cases in the dapagliflozin arm received dapagliflozin treatment for more than 20 months, and the decline in kidney function in these two patients was likely associated with the underlying disease.

Subgroup analyses were performed based on age, gender, race, region, diabetes status at baseline, etiology of CKD (diabetic nephropathy, chronic glomerulonephritis, ischemic/hypertensive neurology, other), eGFR at baseline (<30, 30-<45, 45-<60, ≥60 mL/min/1.73m^2), UACR at baseline (quartile), and SBP at baseline (quartile) (Figure 18.). In general, the results were consistent across most of subgroups with a RD of <0. Compared to the placebo group, the risk of having a renal AE in the dapagliflozin group was slightly higher in patients with an eGFR <30 mL/min/1.73m^2 (RD = 2.5). For more information on safety findings in patients with an eGFR <30 mL/min/1.73m^2, see Section 7.2.4.1.

Figure 18. Renal AEs by Subgroup, Safety Population, DAPA-CKD, On-Treatment Period



Source: Reviewer's analysis, dataset: adsl & adae
Abbreviation: T2DM, type 2 diabetes mellitus, eGFR, estimated glomerular filtration rate, UACR, urine albumin-to-creatinine ratio SBP, systolic blood pressure, D, dapagliflozin, P, placebo, n, number of event, N, number of subject in each group

Events of acute kidney injury (AKI), defined as a doubling of serum creatinine compared to the most recent central laboratory measurement, were adjudicated in DAPA-CKD. Fewer patients in the dapagliflozin group had a positively adjudicated event compared with the placebo group (2.9% vs. 4.2%).

Diabetic Ketoacidosis

Potential DKA events were sent for adjudication in DAPA-CKD. There were 22 patients (1%) in the dapagliflozin group and 20 patients in the placebo group with a potential DKA event that was sent for central adjudication. Two events were adjudicated as definite DKA: both were in the placebo group. In the dapagliflozin group, two events were adjudicated as possible DKA, one in a patient with T2DM and one in a patient who was "pre-diabetic" based on HbA1c (baseline HbA1c ≥ 5.7%). Both events were mild and did not result in a change in the dapagliflozin dose.

Major Hypoglycemic Events

Major hypoglycemia was predefined in DAPA-CKD as an event that requires assistance of another person to actively administer carbohydrates, glucagon, or required other corrective action. The incidence of major hypoglycemic events was higher in the placebo group (n=28, 1.3%) compared to the dapagliflozin group (n=14, 0.7%). The incidence of SAEs of major hypoglycemia was also higher in the placebo group compared to the dapagliflozin group (Table 31). All patients with major hypoglycemic events had diabetes at baseline.

The results of a sensitivity analysis using the FMQ narrow hypoglycemia query are shown in Table 33. The incidence of hypoglycemia was slightly lower in the dapagliflozin group compared with the placebo group, and most events occurred in patients with diabetes at baseline.

Table 33. Incidence of FMQ Narrow Hypoglycemia, Safety Population, DAPA-CKD, On-Treatment Period

	Dapa 10mg		Placebo	
	Non-diabetic (N=696)	Diabetic (N=1453)	Non-diabetic (N=699)	Diabetic (N=1450)
FMQ Hypoglycemia (Narrow)	2 (0.3)	78 (5.4)	2 (0.3)	84 (5.8)
Hypoglycemia	2 (0.3)	76 (5.2)	2 (0.3)	82 (5.7)
Blood glucose decreased	0	2 (0.1)	0	1 (0.1)
Hyperinsulinemic hypoglycemia	0	1 (0.1)	0	1 (0.1)
Shock hypoglycemic	0	0	0	1 (0.1)

Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

Fractures

Adverse events of fracture were analyzed for the on-and off-treatment period. As shown in the table below, the incidence of fracture was similar between the two treatment groups. The most common fractures in the dapagliflozin arm were rib fracture and foot fracture. There were more lower limb fractures in the dapagliflozin group compared to the placebo group.

The risk of bone fracture was also assessed in the DECLARE trial, a larger (N = 17,160) and longer study (median duration of exposure of 48 months). No increased risk of bone fracture was evident in DECLARE. In DECLARE, the incidence of upper limb fracture was slightly higher in the dapagliflozin group compared to the placebo group; however, overall, fractures were distributed across various anatomical locations with no clear pattern indicating an increased frequency at a particular location. The incidence of SAEs was also similar between the two treatment groups (Table 31).

Table 34. Incidence of Fracture AE by Preferred Term, Safety Population, DAPA-CKD, On- and Off-Treatment

	Dapa 10mg (N=2149)	Placebo (N=2149)
FRACTURES	85 (4.0)	69 (3.2)
Rib fracture	12 (0.6)	8 (0.4)
Foot fracture	11 (0.5)	7 (0.3)
Humerus fracture	9 (0.4)	6 (0.3)
Femur fracture	8 (0.4)	4 (0.2)
Tibia fracture	6 (0.3)	2 (0.1)
Ankle fracture	5 (0.2)	3 (0.1)
Lower limb fracture	5 (0.2)	0
Hand fracture	3 (0.1)	8 (0.4)
Spinal compression fracture	3 (0.1)	5 (0.2)

This table only includes preferred terms with a frequency ≥0.2 (N ≥5) in either arm
Source: Reviewer's Table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

Amputations

Adverse events of amputations were analyzed for the on- and off- treatment period. The number of patients who had at least one amputation (excluding one traumatic amputation in the dapagliflozin group) was similar in the two treatment groups: 35 (1.6%) and 39 (1.8%) patients in the dapagliflozin and placebo groups, respectively. Nearly all were surgical amputations, and all involved the lower limb except for one in the dapagliflozin group for which the location was missing/not provided (Table 35). Only one patient without diabetes (in the placebo group) reported a non-traumatic amputation.

Table 35 Amputations by Type and Location, Safety Population, DAPA-CKD, On and Off Treatment

	Dapa 10mg (N=2149)	Placebo (N=2149)
Subjects with at least on amputation	36 (1.7)	39 (1.8)
1 amputation	24 (1.1)	28 (1.3)
2 amputations	9 (0.4)	4 (0.2)
3 amputations	2 (0.1)	4 (0.2)
>3 amputations	1 (0.0)	3 (0.1)
Type of event		
SURGICAL AMPUTATION	34 (1.6)	38 (1.8)
SPONTANEOUS/NON-SURGICAL AMPUTATION	1 (0.0)	1 (0.0)
TRAUMA BY ACCIDENT	1 (0.0)	0
Location of Amputation		
BIG TOE	9 (0.4)	11 (0.5)
BELOW KNEE	7 (0.3)	8 (0.4)
MIDDLE TOE	7 (0.3)	3 (0.1)
ABOVE KNEE	6 (0.3)	12 (0.6)
INDEX TOE	6 (0.3)	4 (0.2)
OTHER	6 (0.3)	9 (0.4)
FOURTH TOE	5 (0.2)	6 (0.3)
LITTLE TOE	4 (0.2)	4 (0.2)
FOOT	0	1 (0.0)
TRANS METATARSAL	0	5 (0.2)
Missing	1 (0.0)	0

Source: Reviewer's Table, dataset: adsl, adae and ce

Information on conditions and contributing factors that triggered amputations was also collected on specific eCRF pages during DAPA-CKD. The most common condition that triggered an amputation was infection in both groups (Table 36). Neuropathy was the most common contributing factor in both groups. There was no difference between groups in signs or symptoms of peripheral artery disease.

Table 36 Conditions and Contributing Factors that Triggered Amputation, Safety Population, DAPA-CKD

	Dapa 10mg (N=2149)	Placebo (N=2149)
Condition that triggered the amputation		
Acute limb ischemia (in setting of PAD of systemic embolism)	2 (0.1)	2 (0.1)
Chronic limb ischemia (dry gangrene, non-healing ischemic ulcer)	4 (0.2)	6 (0.3)
Infection (wet gangrene, non-healing infectious ulcer, osteomyelitis, other infection)	30 (1.4)	32 (1.5)
Contributing factors		
Infection	3 (0.1)	4 (0.2)
Acute limb Ischemia	6 (0.3)	1 (0.0)
Chronic limb Ischemia	6 (0.3)	9 (0.4)
Neuropathy	13 (0.6)	12 (0.6)
Signs or symptoms of PAD since baseline		
PAD at baseline	13 (0.6)	18 (0.8)
No PAD at baseline	22 (1.0)	21 (1.0)

Source: Reviewer's Table, dataset: adsl, adae and ce
Abbreviation: PAD, perihelial artery disease

Reviewer's Comment: The risk of lower limb amputation is included in Section 5 of labeling for other SGLT2 inhibitors including canagliflozin and ertugliflozin. It is thought that SGLT2 inhibitors could, via their diuretic effect, lead to hypoperfusion of extremities in patients at risk of lower limb amputation. The potential risk of amputation has been assessed across the dapagliflozin program, including DECLARE (N = 17,143), DAPA-HF (4,736), and DAPA-CKD (N =4,298). Specifically, amputation was pre-specified as an AESI, and information about amputation events was systematically collected on specific eCRF pages in DAPA-HF and DAPA-CKD. None of the trials excluded patients with a history of amputation or at higher risk for amputation. No strategies were implemented during the trial to decrease the risk of amputation during the study (e.g., discontinuing treatment in patients who developed a condition associated with amputation). In sum, the available data do not suggest that dapagliflozin increases the risk of lower limb amputation.

Adverse Events Leading to a Risk of Lower Limb Amputation

The Applicant pre-specified a group of preferred terms (e.g., various wound/infections, diabetic foot-related AEs, and vascular-related AEs) to identify events that might precede and lead to a risk for amputation.

The incidence of AEs of "preceding events" was slightly higher in the dapagliflozin arm (10.2%) compared to the placebo arm (9.3%), corresponding to event rate of 4.5 and 4.2 per 100

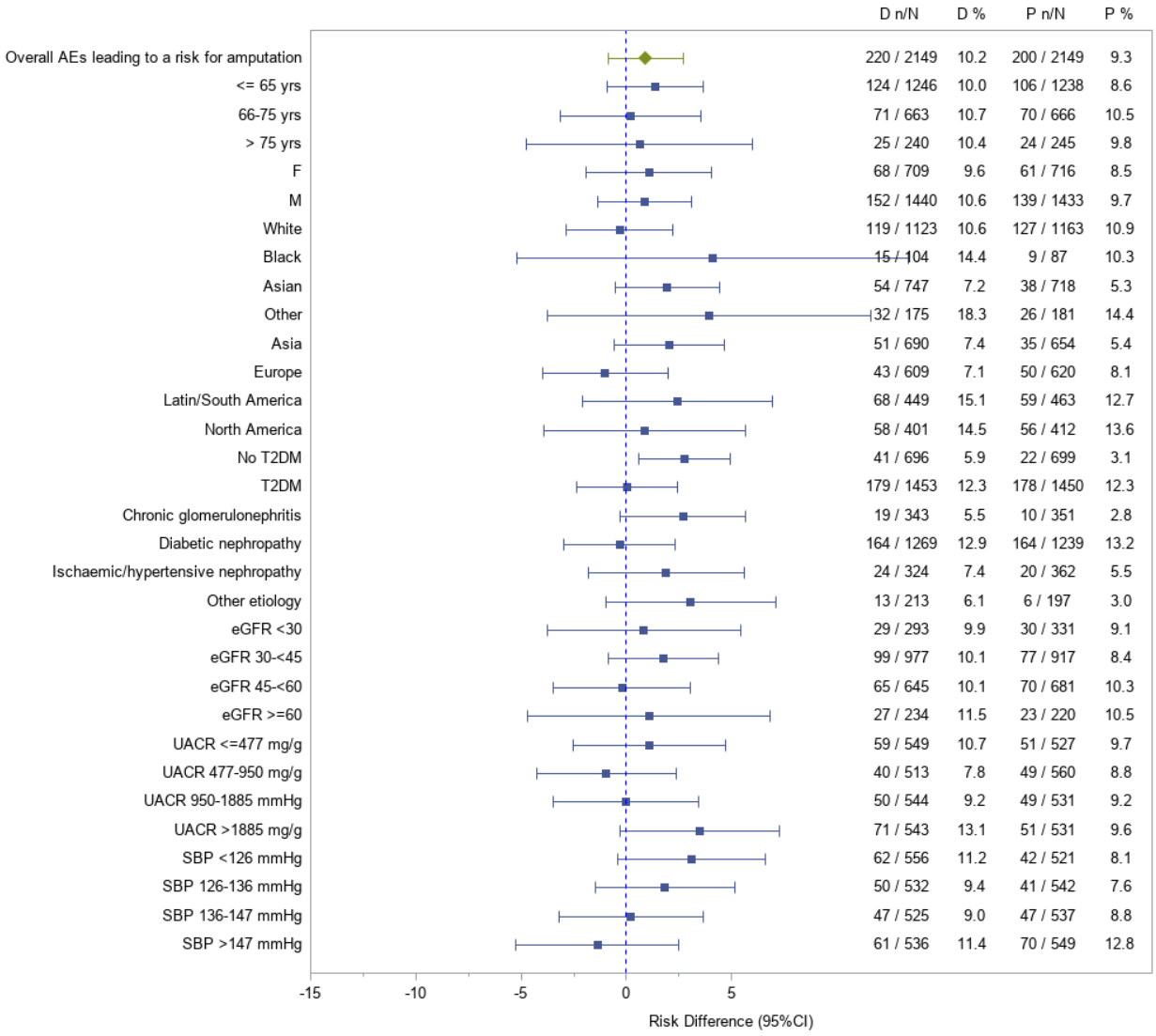
patient-years, respectively. The most common AE in the dapagliflozin group was hypovolemia, a known adverse effect of dapagliflozin (Table 37). Subgroup results were generally consistent with the overall result, indicating a slightly higher incidence of these events in the dapagliflozin group compared to the placebo group (Figure 19.).

Table 37 Incidence of AEs Leading to A Risk for Lower Limb Amputation by Preferred Term, Safety Population, DAPA-CKD, On Treatment

	Dapa 10mg (N=2149)	Placebo (N=2149)
EVENT RELATED TO RISK FOR LOWER LIMB AMPUTATION	212 (9.9)	186 (8.7)
Hypovolemia	37 (1.7)	21 (1.0)
Cellulitis	29 (1.3)	34 (1.6)
Skin ulcer	26 (1.2)	32 (1.5)
Dehydration	17 (0.8)	12 (0.6)
Diabetic foot	14 (0.7)	13 (0.6)
Diabetic neuropathy	13 (0.6)	14 (0.7)
Osteomyelitis	13 (0.6)	11 (0.5)
Peripheral arterial occlusive disease	13 (0.6)	13 (0.6)

This table only include preferred terms with a frequency of >0.5% in either group
Source: Reviewer's Table, dataset: adsl and adae

Figure 19. AEs Leading to A Risk for Amputation by Subgroup, Safety Population, DAPA-CKD, On Treatment Period



Source: Reviewer's analysis, dataset: adsl & adae
Abbreviation: T2DM, type 2 diabetes mellitus, eGFR, estimated glomerular filtration rate, UACR, urine albumin-to-creatinine ratio SBP, systolic blood pressure, D, dapagliflozin, P, placebo, n, number of event, N, number of subjects in each group

Other Safety Events

Genital Infection/Fournier's Gangrene

Genital mycotic infection is an identified adverse reaction for dapagliflozin in patients with T2DM. In DAPA-CKD, genital infection was not one of the pre-defined AESIs, thus non-serious events related to genital infection were only collected if the event led to discontinuation, interruption, or reduction in the dose of study drug. There were 22 (1%) patients (four without diabetes) with at least one reported genital infection AE in the dapagliflozin group and 3 (0.1%) in the placebo group. Most events (>95%) in the dapagliflozin group were with mild to

moderate intensity. A total of 11 subjects in the dapagliflozin group (all with diabetes) had genital infection leading to drug interruption or discontinuation, and there was one in the placebo group. There were three SAEs in the dapagliflozin group; all occurred in patients with diabetes and led to drug interruption or discontinuation. There were no fatal events related to a genital infection.

The Applicant also assessed all SAEs or DAEs possibly indicating Fournier's gangrene based on a specified list of preferred terms. A total of six cases (three from each treatment group) were identified for blinded medical assessment. One event in the placebo group was assessed as Fournier's gangrene (an event reported as anal abscess).

Urinary Tract Infection

Urinary tract infection (UTI) is an identified risk for dapagliflozin in patients with T2DM. Serious urinary tract infections including urosepsis and pyelonephritis are also listed in Section 5 of the approved label for dapagliflozin. UTI was not one of the pre-specified AESIs; therefore, only UTI-related SAEs or AEs leading to discontinuation, interruption, or dose reduction were reported in DAPA-CKD. UTI-related AEs/SAEs in DAPA-CKD were consistent with what is described in the current label (Table 38).

Table 38: Incidence of UTI AEs and SAEs by Preferred Term, Safety Population, DAPA-CKD, On Treatment

	Dapa 10mg (N=2149)	Placebo (N=2149)
UTI related AEs	112 (5.2)	105 (4.9)
UTI related SAEs	29 (1.3)	18 (0.8)
Urinary tract infection	20 (0.9)	13 (0.6)
Pyelonephritis acute	5 (0.2)	1 (0.0)
Cystitis	1 (0.0)	2 (0.1)
Escherichia urinary tract infection	1 (0.0)	0
Pyelonephritis	1 (0.0)	2 (0.1)
Pronephros's	1 (0.0)	0
Urinary tract infection bacterial	1 (0.0)	0
Urogenital infection bacterial	1 (0.0)	0

Source: Reviewer's Table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

Pancreatitis

Pancreatitis is an identified risk for some of SGLT2 inhibitors including canagliflozin and empagliflozin. The risk of pancreatitis, including fatal pancreatitis, was mainly identified through post-marketing data for empagliflozin. Pancreatitis was not an AESI in DAPA-CKD, thus only SAEs or AEs leading to discontinuation, interruption or dose reduction were collected. Table 39 shows the reported pancreatitis AEs in DAPA-CKD; most were SAEs. A higher incidence of pancreatitis AEs was reported in the dapagliflozin group compared to the placebo group. Most events did not result in a dose change and had an outcome of recovered/resolved. There were no fatal cases in either group.

Table 39 Incidence of Pancreatitis by Preferred Term, Safety Population, DAPA-CKD, On-Treatment

	Dapa 10mg (N=2149)	Placebo (N=2149)
Pancreatitis AEs (FMQ)	12 (0.6)	5 (0.2)
PANCREATITIS ACUTE	5 (0.2)	1 (0.0)
PANCREATITIS	4 (0.2)	2 (0.1)
OBSTRUCTIVE PANCREATITIS	2 (0.1)	0
PANCREATITIS CHRONIC	1 (0.0)	2 (0.1)
PANCREATITIS RELAPSING	1 (0.0)	0
Pancreatitis SAEs (FMQ)	11 (0.5)	3 (0.1)
Action taken for study drug		
DOSE NOT CHANGED	9 (0.4)	1 (0.0)
DRUG INTERRUPTED	3 (0.1)	3 (0.1)
NOT APPLICABLE	1 (0.0)	1 (0.0)
Outcome of AEs		
RECOVERED/RESOLVED	10 (0.5)	3 (0.1)
RECOVERED/RESOLVED WITH SEQUELAE	2 (0.1)	0
NOT RECOVERED/NOT RESOLVED	0	2 (0.1)

Source: Reviewer's Table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

From the limited details provided in the case narratives, it is difficult to assess the causal relationship between dapagliflozin and the pancreatitis event. Several cases had a history of cholecystitis, pancreatitis, and/or gallstones, and most continued treatment over years without any recurrence of the event. One patient had a recurrent pancreatitis event during treatment, and one had pancreatitis that was thought to be related to dapagliflozin by the investigator. Brief narratives for these two cases are provided below:

Case #1 ((b) (6)): A 37-years-old Asian male with a history of dyslipidemia and hypertension. He developed stomach pain and nausea on Day 178 and was admitted to the hospital on Day 180. Dapagliflozin was interrupted. No details were provided on his treatment course. He recovered and was discharged on Day 185. Dapagliflozin was resumed on Day 188. The patient experienced abdominal pains and nausea on Day 352 and was admitted to the hospital on Day 355 with a diagnosis of acute pancreatitis. Ultrasonography revealed steatosis, mixed gallstones, and a slightly enlarged pancreas. Dapagliflozin was interrupted. No details were provided on his treatment course. He was discharged on Day 358. Dapagliflozin treatment was restarted on Day 359, and the subject continued treatment to Day 912 and completed the study.

Case #2 ((b) (6)): A 57-year-old white female with a history of T2DM, dyslipidemia, cholecystitis, cholelithiasis, and gallstones. On Day 10, she presented to the emergency department with a two-week history of intermittent and worsening abdominal pain, fever, tachycardia, and a tender abdomen with positive Murphy's sign. She was admitted to the

hospital the same day, and dapagliflozin was interrupted. Blood cultures were positive for *E. coli*, and she was treated with antibiotics. An ultrasound showed cholelithiasis without evidence of acute cholecystitis, common bile duct dilation, and mild hepatic steatosis. The patient was diagnosed with gallstone pancreatitis complicated by cholangitis and underwent laparoscopic cholecystectomy on Day 16. She was discharged on Day 17. The investigator indicated the SAE was possibly related to the study drug. The patients resumed dapagliflozin on Day 27 and continued treatment through Day 979, completing the study.

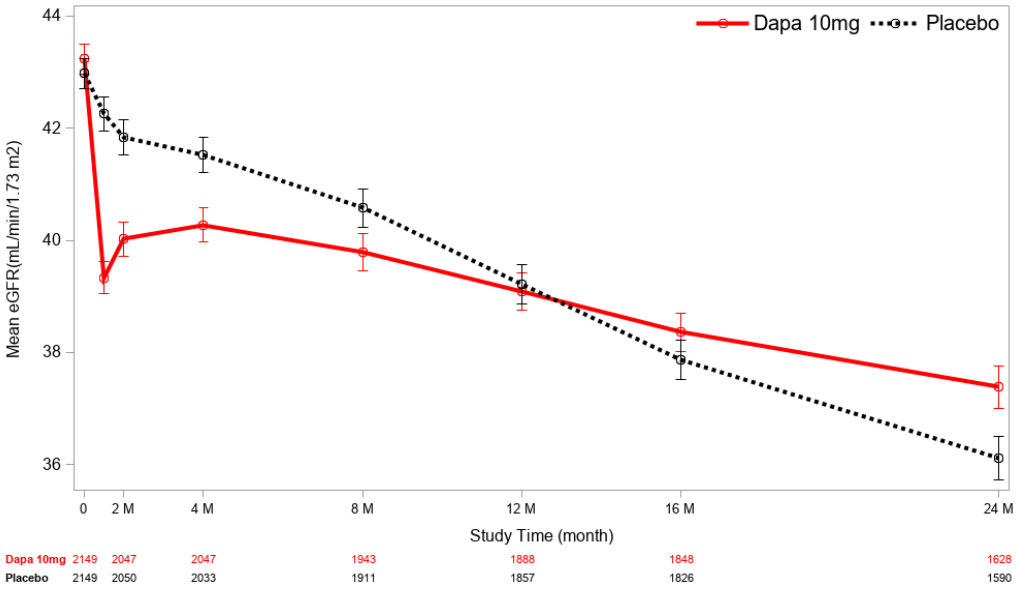
Reviewer's Comment: There was no imbalance in pancreatitis in the original T2DM development program for dapagliflozin or in DECLARE. Specifically, pancreatitis was added as an AESI in DECLARE given the potential risk of pancreatitis with the SGLT2 class. In both DAPA-HF and DAPA-CKD, pancreatitis AEs were reported voluntarily unless they were SAEs or AEs leading to dosing changes. There was no imbalance observed in DAPA-HF. Although the incidence of pancreatitis AEs was slightly numerically greater in the dapagliflozin group compared with placebo in DAPA-CKD, it is not obvious that dapagliflozin played a causal role in these events. Considering the totality of data from all dapagliflozin programs, it is possible that the observed differences are due to chance.

Laboratory Findings

Section 6.1 Clinical Studies Experience of the current label describes increases in serum creatinine, hematocrit, and LDL and decreases in eGFR and serum bicarbonate. In DAPA-CKD, several laboratory parameters were collected at all visits including BUN, serum creatinine, HbA1c, hematocrit, potassium, sodium, and urine albumin and creatinine. Other parameters were collected at least at baseline and the last study visit (i.e., either at the premature treatment discontinuation visit or study closure visit). Overall, no new safety concerns were raised by analyses of laboratory data in DAPA-CKD. For known effects such as increases in hematocrit and creatinine, the results in DAPA-CKD are consistent with the descriptions in the current label. Analyses of kidney function and hematocrit are described below.

In DAPA-CKD, there was an initial small rise in serum creatinine and a corresponding decrease in eGFR in the dapagliflozin arm. The changes peaked by week 2 after initiation of therapy. This time-course was observed regardless of kidney function status at baseline (see Appendix 12.10 Figure 37-Figure 40 for eGFR change over time by baseline eGFR).

Figure 20. Average eGFR over Time, Safety Population, DAPA-CKD



Source: Reviewer's analysis, dataset: adsl & adlb

A small mean increase (~1-2%) in hematocrit was observed following the initiation of dapagliflozin; the increase was observed shortly after initiation then plateaued after Month 4 (difference of approximately 2%). A higher percentage of patients in the dapagliflozin arm (13.4%) vs. the placebo arm (6.1%) had at least one hematocrit value >55% during the study.

Vital Signs

As reported for previous studies, there was a small decrease in body weight and SBP in the dapagliflozin group compared to the placebo group. The mean difference between treatment groups ranged from -2.2 to -3.7 mmHg for SBP and -0.5 to -1.0 kg for body weight. The observed changes are consistent with the glycosuric and diuretic effects of dapagliflozin.

Electrocardiograms (ECGs)

Electrocardiograms were only measured at randomization in DAPA-CKD. There were no safety concerns or clinically relevant rhythm differences observed in the ECG data from patients with T2DM submitted with the original NDA for dapagliflozin.

QT

No clinically meaningful differences in QTc intervals were observed between placebo and dapagliflozin 20 mg or 150 mg doses in the thorough QT study (D1690C00001) reviewed with the original NDA.

Immunogenicity

Immunogenicity was not assessed in DAPA-CKD. However, there is no safety concern regarding immunogenicity from previous trials.

Analysis of Submission-Specific Safety Issues

7.2.4.1. Risk Profile in Patients with eGFR <30 mL/min/1.73m^2

Issue: DAPA-CKD included patients with an eGFR <30 mL/min/1.73m^2, a population that has not been studied in other dapagliflozin trials. It is known that there is a 2.4-fold increase in dapagliflozin exposure for patients with an eGFR <30 mL/min/1.73m^2 compared to patients with normal kidney function. Whether the risk profile in this subset was consistent with the overall population was a safety review issue.

Assessment: Approximately 14% of patients enrolled in DAPA-CKD had a baseline eGFR <30 mL/min/1.73m^2. The trial excluded patients with a screening eGFR <25 mL/min/1.73m^2; however, given how baseline was defined, a few had a baseline eGFR <25 mL/min/1.73m^2 (n= 29 in the dapagliflozin group). The overall safety profile in this subgroup of patients was generally consistent with that of the overall population (Table 40). The incidence of renal AEs and the number of patients with AEs leading to dose interruption or dose reduction were slightly higher in the dapagliflozin group compared with the placebo group in this subset. Additional analyses and discussion of these findings are described below:

<u>Renal AEs</u>
The severity and outcome of the renal events by baseline kidney function are summarized in Table 41. In the subgroup of patients with a baseline eGFR <30 mL/min/1.73m^2, renal impairment AEs were reported more frequently in patients treated with dapagliflozin than placebo; however, the events were generally categorized as mild. Subgroup analyses using FMQ acute kidney injury (narrow or broad) show that the results in patients with an eGFR <30 mL/min/1.73m^2 are generally consistent with the overall result and did not raise a major safety concern (Appendix 12.10 Table 61).

Reviewer's Comment: Renal events that met criteria for efficacy endpoints were reported on a designated eCRF page. There were no pre-specified definitions or specific eCRF pages for reporting a renal AE. The Applicant used MedDRA SMQ acute renal failure (narrow) to assess renal AEs, which does not include AEs associated with changes in laboratory parameters. The imbalance in renal AEs between groups among subjects with an eGFR <30 mL/min/1.73m^2 was primarily driven by a higher incidence of AEs of "renal impairment" in the dapagliflozin group as compared to the placebo group. Most of these AEs were mild to moderate intensity, which could simply reflect changes in renal laboratory parameters.

The FMQ acute kidney injury includes the preferred term renal impairment in the broad definition but not in the narrow definition. In analyses that included both AEs related to renal impairment and AEs related to laboratory changes, such as serum creatinine increase and eGFR decreased (FMQ acute renal injury, broad), there was no difference between the groups among patients with a baseline eGFR <30 mL/min/1.73m^2. In addition, there was a lower incidence of adjudicated AKI events in the dapagliflozin group compared with the placebo group among patients with a baseline eGFR <30 mL/min/1.73m^2 (3.8% vs. 5.7%), consistent with the results in the overall population.

Table 40 Overview of Adverse Events in Categories of Interest in Subjects with eGFR <30 mL/min/1.73m^2

	eGFR < 30 mL/min/1.73m^2		Safety Population	
	Dapa 10mg (N=293)	Placebo (N=331)	Dapa 10mg (N=2149)	Placebo (N=2149)
Deaths	14 (4.8)	19 (5.7)	73 (3.4)	100 (4.7)
SAE	93 (31.7)	123 (37.2)	594 (27.6)	674 (31.4)
Volume depletion related AEs	13 (4.4)	14 (4.2)	120 (5.6)	84 (3.9)
Renal AEs (SMQ acute renal failure, narrow)	42 (14.3)	39 (11.8)	144 (6.7)	169 (7.9)
Major hypoglycemic AEs	2 (0.7)	8 (2.4)	14 (0.7)	18 (1.3)
Fracture	11 (3.8)	15 (4.5)	85 (4.0)	69 (3.2)
Amputation	3 (1.0)	4 (1.2)	36 (1.7)	39 (1.8)
AEs leading to drug discontinuation	28 (9.6)	36 (10.9)	118 (5.5)	123 (5.7)
Acute renal injury (SMQ, broad)[a]	12 (4.1)	13 (3.9)	27 (1.3)	31 (1.4)
Chronic renal disease/end stage kidney disease	6 (2.0)	5 (1.5)	16 (0.7)	14 (0.7)
UTI	1 (0.3)	0	8 (0.4)	3 (0.1)
Volume depletion related AEs	0	0	4 (0.2)	1 (0.0)
Hypoglycemia	0	1 (0.3)	0	2 (0.1)
AEs leading to dose interruption and reduction	53 (18.1)	49 (14.8)	303 (14.1)	294 (13.7)
Acute renal injury (SMQ, broad)[a]	10 (3.4)	17 (5.1)	49 (2.3)	60 (2.8)
Chronic renal disease /end stage disease	8 (2.7)	7 (2.1)	16 (0.7)	14 (0.7)
UTI	5 (1.7)	2 (0.6)	20 (0.9)	12 (0.6)
Volume depletion related AEs	3 (1.0)	0	23 (1.1)	10 (0.5)
Hypoglycemia	4 (1.4)	2 (0.6)	9 (0.4)	7 (0.3)

Source: Reviewer's Table, dataset: adsl & adae
[a]Acute renal injury related events including adverse changes in renal laboratory parameters that led to dosing changes

Table 41 Renal Adverse Events by Baseline eGFR, Safety Population, DAPA-CKD, On Treatment

	Dapa 10mg				Placebo			
	<30 (N=293)	30-<45 (N=977)	45-<60 (N=645)	≥ 60 (N=234)	<30 (N=331)	30-<45 (N=917)	45-<60 (N=681)	≥ 60 (N=220)
Renal AE (SMQ, Acute Renal Failure, narrow)	42 (14.3)	61 (6.2)	28 (4.3)	13 (5.6)	39 (11.8)	72 (7.9)	44 (6.5)	14 (6.4)
Renal impairment	22 (7.5)	22 (2.3)	9 (1.4)	5 (2.1)	18 (5.4)	27 (2.9)	16 (2.3)	10 (4.5)
Acute kidney injury	16 (5.5)	35 (3.6)	18 (2.8)	5 (2.1)	18 (5.4)	35 (3.8)	25 (3.7)	3 (1.4)
Renal failure	4 (1.4)	4 (0.4)	2 (0.3)	1 (0.4)	4 (1.2)	6 (0.7)	4 (0.6)	0
Nephropathy toxic	2 (0.7)	0	0	1 (0.4)	0	3 (0.3)	0	1 (0.5)
Azotemia	0	0	0	0	0	0	1 (0.1)	0
Prerenal failure	0	0	0	1 (0.4)	0	2 (0.2)	1 (0.1)	0
Severity								
MILD	13 (4.4)	20 (2.0)	8 (1.2)	3 (1.3)	3 (0.9)	18 (2.0)	14 (2.1)	5 (2.3)
MODERATE	23 (7.8)	23 (2.4)	18 (2.8)	8 (3.4)	25 (7.6)	39 (4.3)	24 (3.5)	5 (2.3)
SEVERE	12 (4.1)	18 (1.8)	5 (0.8)	2 (0.9)	13 (3.9)	18 (2.0)	11 (1.6)	5 (2.3)
Outcome								
RECOVERED/RESOLVED	28 (9.6)	40 (4.1)	23 (3.6)	7 (3.0)	21 (6.3)	46 (5.0)	32 (4.7)	11 (5.0)
NOT RECOVERED/NOT RESOLVED	14 (4.8)	12 (1.2)	5 (0.8)	5 (2.1)	15 (4.5)	16 (1.7)	14 (2.1)	3 (1.4)
RECOVERING/RESOLVING	3 (1.0)	5 (0.5)	0	1 (0.4)	0	6 (0.7)	4 (0.6)	0
RECOVERED/RESOLVED WITH SEQUELAE	2 (0.7)	3 (0.3)	1 (0.2)	0	4 (1.2)	7 (0.8)	0	0
FATAL	1 (0.3)	1 (0.1)	0	0	1 (0.3)	0	0	0

Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool

Analyses were also conducted to evaluate the timing of these events, given that dapagliflozin causes an acute, reversible hemodynamic effect on eGFR which may not reflect true injury to the kidney. On a trial level, this manifests as small increases in serum creatinine and decreases in eGFR within two weeks of starting therapy that then stabilizes. These trends were observed regardless of baseline kidney function (see laboratory findings and Appendix Figure 37-Figure 40).

Among patients with lower baseline kidney function, renal AEs (FMQ acute renal injury, narrow) across study timepoints were summarized by baseline eGFR (Table 42). There were no acute kidney injury related AEs within 2 weeks of starting therapy in any of the subgroups. Analyses of renal AEs across study time points based on the FMQ acute kidney injury (broad) are summarized in Appendix 12.10 Table 62.

Table 42 Renal Adverse Events Assessed by FMQ by Baseline eGFR across Study Time Points, Safety Population, DAPA-CKD, On Treatment

	Dapa 10mg				Placebo			
	<30 (N=293)	30-<45 (N=977)	45-<60 (N=645)	≥ 60 (N=234)	<30 (N=331)	30-<45 (N=917)	45-<60 (N=681)	≥ 60 (N=220)
Acute renal injury AEs (FMQ narrow) [a]	18 (6.1)	37 (3.8)	18 (2.8)	7 (3.0)	18 (5.4)	41 (4.5)	26 (3.8)	5 (2.3)
>0.5-2 M	3 (1.0)	3 (0.3)	2 (0.3)	0	2 (0.6)	0	1 (0.1)	1 (0.5)
>2-4 M	1 (0.3)	6 (0.6)	7 (1.1)	1 (0.4)	3 (0.9)	3 (0.3)	6 (0.9)	1 (0.5)
>4-8 M	2 (0.7)	3 (0.3)	2 (0.3)	0	2 (0.6)	7 (0.8)	3 (0.4)	0
>8-12 M	2 (0.7)	4 (0.4)	4 (0.6)	2 (0.9)	1 (0.3)	5 (0.5)	3 (0.4)	0
>12-16 M	4 (1.4)	5 (0.5)	2 (0.3)	1 (0.4)	3 (0.9)	6 (0.7)	5 (0.7)	2 (0.9)
>16-20 M	2 (0.7)	5 (0.5)	0	0	3 (0.9)	6 (0.7)	0	0
>20-24 M	1 (0.3)	3 (0.3)	1 (0.2)	2 (0.9)	2 (0.6)	8 (0.9)	3 (0.4)	0
>24-28 M	3 (1.0)	6 (0.6)	0	1 (0.4)	2 (0.6)	1 (0.1)	4 (0.6)	1 (0.5)
>28-32 M	0	1 (0.1)	0	0	0	4 (0.4)	1 (0.1)	0
>0.5-2 M	0	1 (0.1)	0	0	0	1 (0.1)	0	0
Acute renal injury SAEs (FMQ narrow) [a]	10 (3.4)	17 (1.7)	7 (1.1)	3 (1.3)	10 (3.0)	29 (3.2)	10 (1.5)	2 (0.9)
>0.5-2 M	2 (0.7)	2 (0.2)	1 (0.2)	0	1 (0.3)	0	1 (0.1)	1 (0.5)
>2-4 M	1 (0.3)	4 (0.4)	3 (0.5)	1 (0.4)	1 (0.3)	3 (0.3)	4 (0.6)	0
>4-8 M	0	0	1 (0.2)	0	2 (0.6)	3 (0.3)	0	0
>8-12 M	2 (0.7)	1 (0.1)	1 (0.2)	2 (0.9)	1 (0.3)	3 (0.3)	1 (0.1)	0
>12-16 M	1 (0.3)	2 (0.2)	1 (0.2)	0	0	4 (0.4)	1 (0.1)	1 (0.5)
>16-20 M	1 (0.3)	1 (0.1)	0	0	1 (0.3)	4 (0.4)	0	0
>20-24 M	0	0	0	0	2 (0.6)	6 (0.7)	1 (0.1)	0
>24-28 M	3 (1.0)	6 (0.6)	0	0	2 (0.6)	1 (0.1)	1 (0.1)	0
>28-32 M	0	1 (0.1)	0	0	0	4 (0.4)	1 (0.1)	0
>0.5-2 M	0	0	0	0	0	1 (0.1)	0	0

a. No AEs and SAEs occurred within 2 weeks after initiation of the study drug in both groups
Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool
Abbreviation: M, month

AEs leading to dose interruptions and dose reductions

Although there was a greater incidence of AEs leading to dose reduction/dose interruption for dapagliflozin compared to placebo among patients with an eGFR <30 mL/min/1.73m^2 (18.1% vs. 14.8%), the differences were based on small numbers of events, and there were no particular AEs driving the result. Renal-related AEs were the most common AEs leading to dose changes in this subgroup as well as in the overall population, and there was no difference between dapagliflozin and placebo.

Conclusion:

The safety profile in patients with an eGFR <30 mL/min/1.73m^2 appears to be consistent, as a whole, with the known safety profile of dapagliflozin; however, there are limited safety data among patients with an eGFR <25 mL/min/1.73m^2.

7.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

7.2.6. Safety Analyses by Demographic Subgroups

The risk profile of dapagliflozin in patients with CKD is consistent across demographic subgroups. Demographic subgroups including age, sex, and race were performed for deaths, SAEs and AESIs (see Section 7.2.4).

7.2.7. Specific Safety Studies/Clinical Trials

Not applicable.

7.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans (see Section 13.1 of the current label).

Human Reproduction and Pregnancy

Section 8.1 Pregnancy of the current label states dapagliflozin is not recommended during the second and third trimesters of pregnancy based on animal data. Pregnant patients were excluded from participating in the DAPA-CKD study. There were eight pregnancies reported during the study (two in the dapagliflozin group and six in the placebo group). Of the two pregnancies in the dapagliflozin group, one was an anembryonic pregnancy that was reported as an SAE, and one was terminated through elective abortion.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of dapagliflozin has not been established in pediatric patients under 18 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No events of overdose of study drug were reported during the DAPA-CKD study or other clinical development programs for dapagliflozin.

7.2.9. Safety in the Postmarket Setting

Dapagliflozin was first approved for the treatment of patients with T2DM in Australia in 2012 and in the US in 2014. It is currently approved in over 100 countries. The latest dapagliflozin Periodic Benefit-Risk Evaluation Report dated 20 November 2020 with a data lock date of 04

October 2020 included more than (b) (4) patient-years of post-marketing exposure. There was no new safety signal or information that would alter the known benefit-risk profile of dapagliflozin for the approved indications.

7.2.10. Integrated Assessment of Safety

The safety evaluation of dapagliflozin based on the DAPA-CKD trial was adequate and acceptable for the proposed indication. Treatment with dapagliflozin 10 mg daily was well tolerated in the CKD population with fewer SAEs and AEs with an outcome of death in the dapagliflozin group than in the placebo group. The numbers of AEs leading to study drug discontinuation, dose interruption, and dose reduction were similar between groups. Approximately 5.5% of patients in each arm discontinued study drug because of an AE. The most common reason for study drug discontinuation was a renal-related event; the incidence was similar between treatment groups (< 1.5% in either group). Volume depletion occurred more frequently with dapagliflozin than placebo (6% vs. 4%) with no difference between groups for reported SAEs (0.7% in both groups). AEs leading to a risk for lower limb amputation also were more frequent in the dapagliflozin group, largely driven by hypovolemia events (10.2% vs. 9.3%); however, there was no difference between groups in amputations. There were also no differences between groups for other AESIs including DKA and fractures. Fewer renal AEs were reported in the dapagliflozin group compared to the placebo group (6.7% vs. 7.9%).

The safety profile is in general consistent across subgroups of interest including demographic characteristics and important clinical characteristics such as diabetes status and baseline kidney function. Specifically, the overall safety profile in the subgroup of subjects with an eGFR <30 mL/min/1.73m^2 was generally consistent with the results for the overall population, although the number of patients in this subgroup was limited, particularly those with an eGFR <25 mL/min/1.73m^2.

7.3. Statistical Issues

Statistical issues for DAPA-CKD are discussed together with clinical issues in Section 7.1.6 of the review. Statistical issues for DECLARE have been previously discussed and are not addressed here.

7.4. Conclusions and Recommendations

See Section 1.

8 Advisory Committee Meeting and Other External Consultations

The application did not raise significant issues regarding the safety or effectiveness of the drug;

hence, no Advisory Committee meeting was convened for this application.

9 Pediatrics

No new pediatric data were submitted with this application.

Each of the two proposed indications proposed in supplement 024 would trigger PREA; however, pediatric assessments will be waived in all age groups because studies would be impossible or highly impractical:

- *To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death in patients with CKD at risk of progression*: Given the unmet need for approved therapies and challenges designing an adequately powered, feasible clinical trial in pediatric patients with CKD, (b) (4) it is not clear a feasible pediatric clinical trial can be conducted at present.
- *To reduce the risk of hospitalization for heart failure in patients with CKD:* heart failure in pediatric patients with CKD is rare and studies would be impossible or highly impractical.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Members of the review team worked closely with Mike Monteleone, Associate Director for Labeling, and the Division of Diabetes, Lipids, and Obesity on revisions to the dapagliflozin label. Relevant sections of labeling were also reviewed by clinical pharmacology. Highlights include the following:

- *Indications and Clinical Studies:* The Indications and Clinical Studies sections were updated to include the new indication and a description of the DAPA-CKD trial (Section 14.4). Editorial updates were made to descriptions of the DECLARE trial in Section 14.2; however, no new data were added to that section. A statement was added to Section 14.4

referencing exploratory analyses of DECLARE data that supported a broader indication based on the findings of DAPA-CKD.

- *Dosing and Administration:* (b) (4) single table that provides dosing recommendations based on both indication and eGFR.

- *Adverse Reactions and Special Populations:* The Adverse Reactions and Special Populations sections of the label were updated to add the DAPA-CKD trial population and to note that the safety findings in DAPA-CKD were similar to the findings in other trials.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed prescribing information and medication guide for areas of vulnerability that may lead to medication errors and provided recommendations to improve clarity.

11 Postmarketing Requirements and Commitment

There are no new postmarketing requirements and commitments.

12 Appendices

12.1. References

See footnotes in body of review.

12.2. Financial Disclosure

The Applicant has adequately disclosed financial arrangements of clinical investigators as recommended. There were only three investigators with disclosable financial interests who had significant financial contributions (>$25,000). In total, the three sites affected (b) (6) made up ~1% of the randomized population and contributed a total of four primary efficacy events. Because DAPA-CKD was a double-blind trial and the overall number of patients enrolled in the three sites with large financial interests was small, the findings from these studies are unlikely to affect the overall trial findings.

Covered Clinical Study (Name and/or Number): DAPA-CKD

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1765		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

12.3. OCP Appendices: Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of descriptive labeling of dapagliflozin PK in the CKD population and characterizing the relationship of eGFR on dapagliflozin apparent CL. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. The Applicant's conclusions that no meaningful differences in dapagliflozin PK between CKD patients with and without T2DM is acceptable.

1.2 Introduction

The primary objectives of Applicant's analysis were to:

- Characterize the structural pharmacokinetic (PK) model and quantify the population variability in the PK parameters of dapagliflozin.
- Describe the effects of intrinsic and/or extrinsic factors on dapagliflozin exposure including CKD patients with or without type 2 diabetes mellitus.

1.3 Model development

Data

The analysis was based on PK data from 7 studies. The study design, study population, and timing of blood samples varied among the 7 clinical studies. Brief descriptions of the studies included are presented in Table 18.1-1

The final NONMEM data file for analysis contained *9715* PK observations from *3055* subjects. Table 18.1-2 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 18.1-1 Summary of Studies with PK Sampling Included in Population PK Analysis

Study number	Study description	Doses	Number of subjects with PK sampling	Population	PK sampling times
CKD study					
DAPA-CKD	Randomised, double-blind, placebo-controlled, parallel group, multicentre, Ph3 outcomes study	10 mg (5 mg if needed)[a]	1801	CKD	1 pre-dose concentration at week 52
Adult T2DM and healthy subject studies					
MB102002	Ascending multiple-dose study	2.5, 10, 20, 50 and 100 mg once daily	30	Healthy subjects	Day 1, 7 and 14: Up to 14 serial measurements post-dose. Trough samples up to day 27.
MB102003	Randomised, double-blind, placebo-controlled, parallel group, Ph2.	5, 25 and 100 mg once daily	39	Adult T2DM	Day 1 and 14: Up to 14 serial measurements. Trough samples up to day 14.
MB102013	Randomised, double-blind, placebo-controlled, parallel group, Multicentre, Ph3	2.5, 5 and 10 mg once daily	480	Adult T2DM	Day 1 and week 20: pre-dose and 60 min and 180 min post-dose. Week 16, 20 and 24: pre-dose.
D1690C00006	Randomised, double-blind, placebo-controlled, parallel group, Multicentre, Ph3	2.5, 5 and 10 mg once daily	567	Adult T2DM	Week 8 and 20: pre-dose, 60 and 180 min post-dose
MB102032	Randomised, double-blind, placebo-controlled, parallel group, Multicentre, Ph3	1, 2.5 and 5 mg	183	Adult T2DM	Week 20: pre-dose, 30, 60, 120 and 180 min post-dose
Paediatric T2DM study					
MB102091	Randomised, multicenter, parallel group, single dose study	2.5, 5 and 10 mg single dose	24	Paediatric T2DM	Up to 11 serial PK samples for 2 days post-dose

(Source: Applicant's Population PK report, Table 1)

Table 18.1-2. Summary of Baseline Demographic Covariates for Analysis

Variable	All subjects	DAPACKD without DM	DAPACKD with T2DM	T2DM	Paediatric T2DM	Healthy subjects
n	3055	560	1218	1223	24	30
Age [years] - (median [range])	60 [11, 93]	58 [23, 91]	65 [31, 93]	57 [18, 79]	15 [11, 17]	34 [25, 42]
Bodyweight [kg] - (median [range])	84 [39, 168]	78 [40, 145]	81 [39, 158]	90 [42, 164]	94 [61, 168]	80 [66, 99]
eGFR - (median [range])	56 [19, 154]	40 [23, 78]	42 [19, 86]	90 [32, 154]	110 [82, 154]	107 [76, 121]
Body mass index [(kg/m2)] - (median [range])	30 [16, 66]	27 [17, 50]	30 [16, 66]	32 [17, 47]	36 [23, 52]	26 [22, 33]
Males - n (%)	1828 (59.8)	390 (69.6)	795 (65.3)	604 (49.4)	9 (37.5)	30 (100.0)
Race - n (%)						
Caucasian	2134 (69.9)	331 (59.1)	645 (53.0)	1132 (92.6)	11 (45.8)	15 (50.0)
Black	143 (4.7)	22 (3.9)	67 (5.5)	30 (2.5)	11 (45.8)	13 (43.3)
Asian	609 (19.9)	184 (32.9)	378 (31.0)	46 (3.8)	0 (0.0)	1 (3.3)
Other	169 (5.5)	23 (4.1)	128 (10.5)	15 (1.2)	2 (8.3)	1 (3.3)
CKD stage - n (%)						
eGFR 15-29	229 (7.5)	80 (14.3)	149 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)
eGFR 30-44	821 (26.9)	271 (48.4)	537 (44.1)	13 (1.1)	0 (0.0)	0 (0.0)
eGFR 45-59	613 (20.1)	159 (28.4)	373 (30.6)	81 (6.6)	0 (0.0)	0 (0.0)
eGFR 60-89	739 (24.2)	50 (8.9)	159 (13.1)	523 (42.8)	2 (8.3)	5 (16.7)
eGFR > 90	653 (21.4)	0 (0.0)	0 (0.0)	606 (49.6)	22 (91.7)	25 (83.3)

(Source: Applicant's Population PK Report, Table 3)

Base model

The base model was the previous final population PK model from the T2DM population.

The base model was a two-compartment PK model, first-order absorption, and first-order elimination from the central compartment. Inter-individual variability (IIV) was estimated on CL/F and Vp/F. During model development, IIV was fixed for Ka to the model estimated value from the previous T2DM population PK model. Consistent with the previous final model, the effect of weight was estimated as an allometric exponent on Vc/F. The effect of eGFR and Sex were estimated on CL. The covariate relationships are shown in the following equations.

$$\frac{CL}{F} = \frac{\theta CL_{REF}}{F} * \left(\frac{eGFR}{eGFR_{REF}}\right)^{\theta eGFR \sim CL} * exp(\theta SEX \sim CL * (1 - SEXM))$$

$$\frac{Vc}{F} = \frac{\theta Vc_{REF}}{F} * \left(\frac{BWT}{BWT_{REF}}\right)^{\theta BWT \sim CL}$$

Inter-individual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Reviewer's Comments:

The Applicant's population PK model (base model in this submission) was reviewed previously by the division of pharmacometrics and found to be acceptable for descriptive labeling purposes of dapagliflozin the T2DM population.

Covariate analysis

From the Applicant's Population PK Report, Section 6.3 Model Building:

(b) (4)

1.4 Final Model

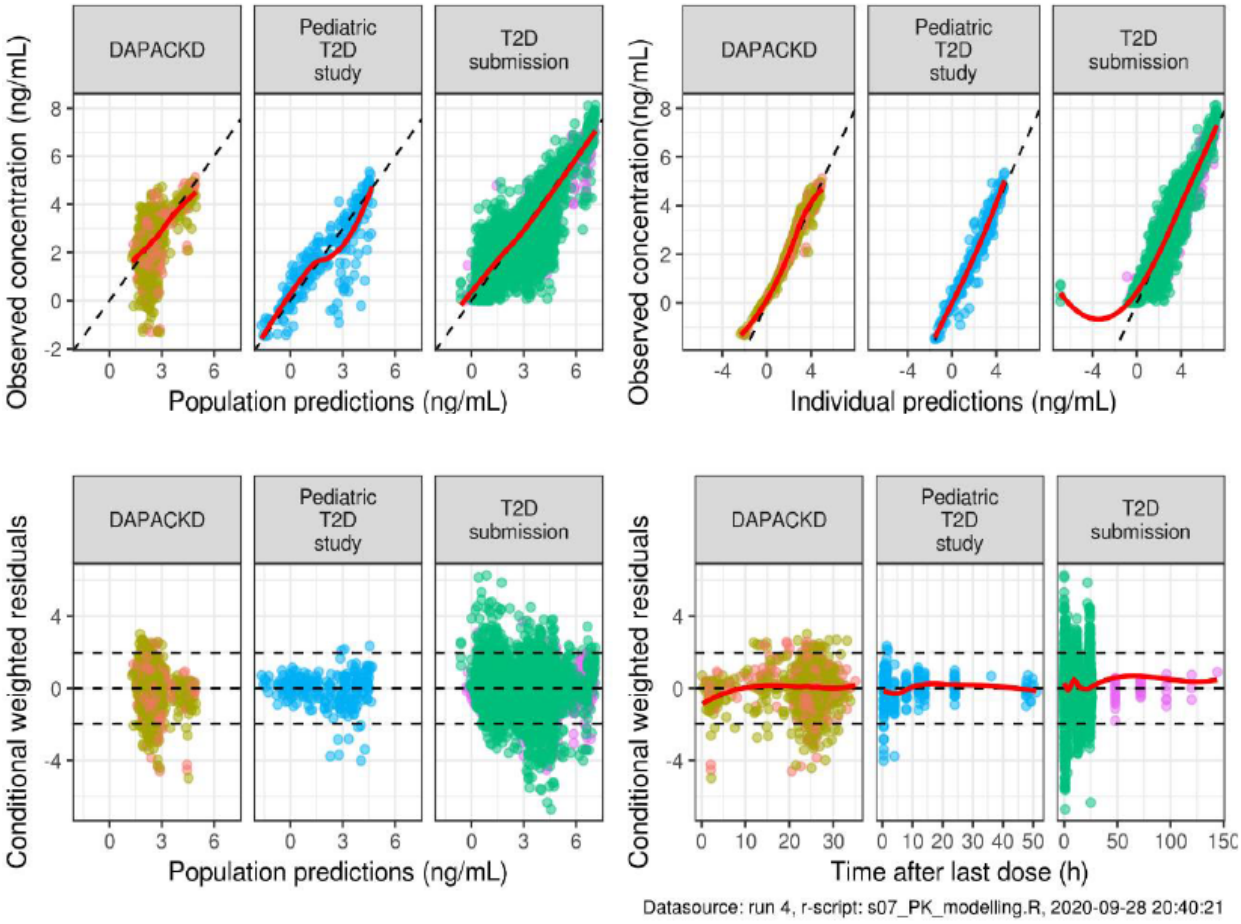
The parameter estimates for the final covariate model are listed in Table 18.1-3. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 18.1-1. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure 18.1-2.

Table 18.1-3. Parameter Estimates and RSE for the Final Model

OFV: -1732.921			
Condition number: 50500			
Parameters	**Units**	**Population Mean**	**RSE (%)**
KA	(h^{-1})	2.833	2.300
CL/F	(L/h)	21.56	1.400
Vc/F	(L)	73.47	1.500
Vp/F	(L)	168.5	8.000
Q/F	(L/h)	9.137	2.600
eGFR~CL/F	(-)	0.6374	3.300
SEX~CL/F	(-)	-0.1441	11.700
BWT~Vc/F	(-)	0.5424	12.700
EPI	(-)	0.5491	6.000
Between Subject variability			
CL/F	(-)	0.1136	4.200
Vp/F	(-)	0.8229	12.400
Residual variability			
Add Error (adults)	(-)	0.1849	0.800
Prop Error (adults)	(-)	0.2845	14.100
Prop Error (paediatrics)	(-)	0.2519	6.600
Datasource: run 4, r-script: s07_PK_modelling.R, 2020-09-28 20:41:04			

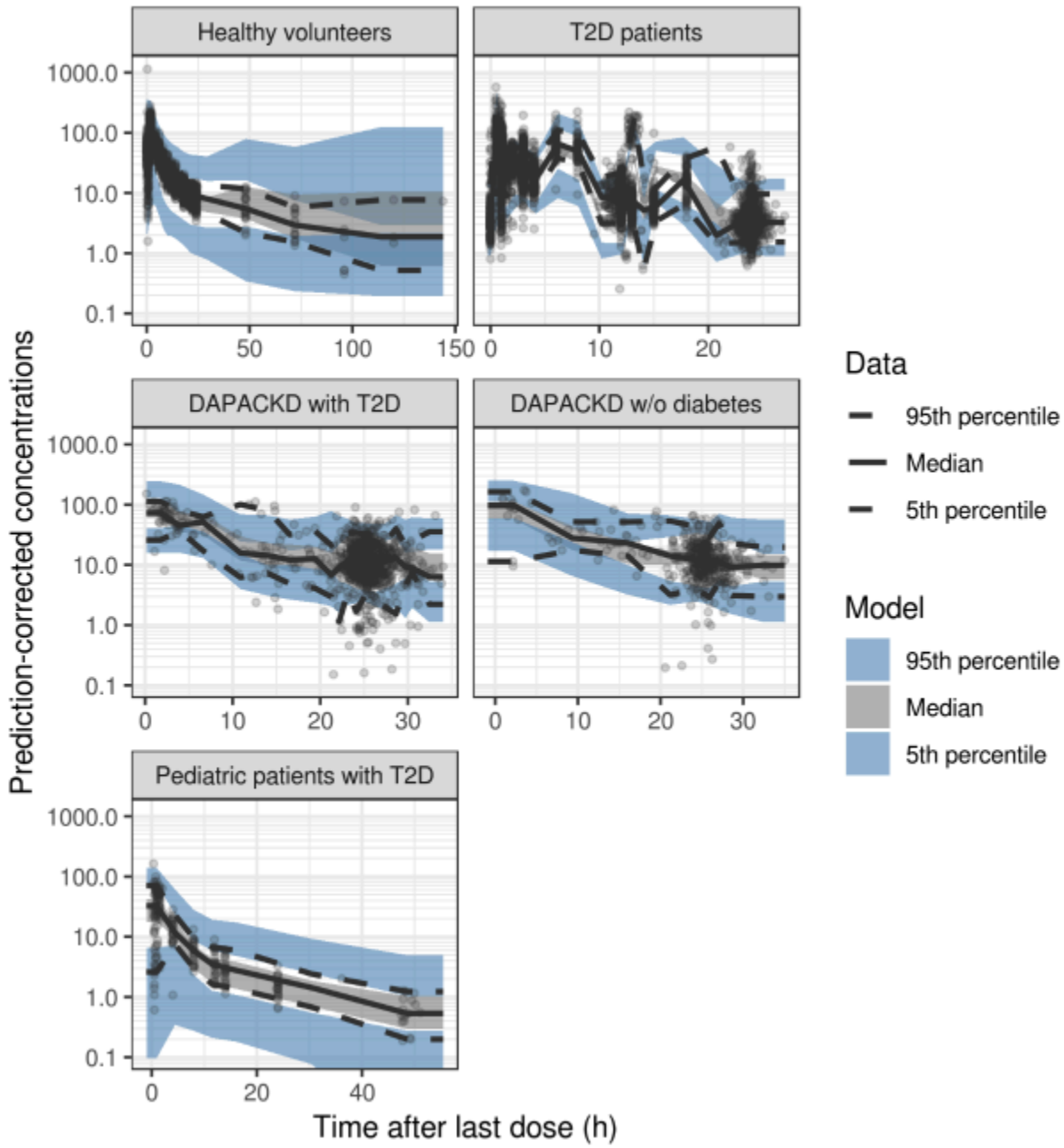
(Source: Applicant's Population PK Report, Figure 5)

Figure 18.1-1. Goodness-of-fit plots for final covariate model by population



The black line in the DV vs PRED/IPRED plots represents the line of unity (y=x). The center dashed black line in the CWRES vs PRED/TIME plots represents the horizontal line (y=0). The red line represents a smooth regression line.
Source: Applicant's Population PK Report, Figure F-1

Figure 18.1-2. Prediction-corrected VPC plots for the final covariate model by patient population



(Source: Applicant's Population PK Report, Figure 8)

12.4. Trial conduct

Table 43 Time course of changes to protocol, SAP, data handling, and committee charters for DAPA-CKD

	2016	2017						2018						2019						2020				
Numerical month in a year	10 11 12	1 2	3 4	5 6	7 8	9 10	11 12	1 2	3 4	5 6	7 8	9 10	11 12	1 2	3 4	5 6	7 8	9 10	11 12	1 2	3 4	5 6	7 8	9 10
Patient flow: **FPFV:** first patient first visit **LPLV**: last patient last visit		**FPFV** Feb 2																				**LPLV** June 12		
Global protocol changes **V:** version **E:** No. enrolled **R:** No randomized **EE**: endpoint events	**V1** Oct 26 E: 0 R:0 EE: 0					**V2** Sep 26 E:2267 R:1165 EE:8														**V3** Jan 22 E: 7409 R: 4225 EE:453	**V4** Mar 17 E:7473 R: 4261 EE: 497			
SAP changes **V:** version **E:** No. enrolled **R:** No randomized **EE**: end point events		**V1** Feb 1 E: 0 R: 0 EE:0																			**V2** Apr 15 E:7517 R: 4304 EE: 509			
DL: Database lock S: Study stop^ **SED:** Study end date																					**S** Mar 26 **SED** April 3		**DL** July 17	
EC charter **V:** version		**V1** Feb 27																						
CEA charter **V:** version			**V1*** Apr3																	**V2** Feb 14				
DMC charter **V:** version		**V1** Jan 29																						
NLC charter **V:** version		**V1** Feb 1																						

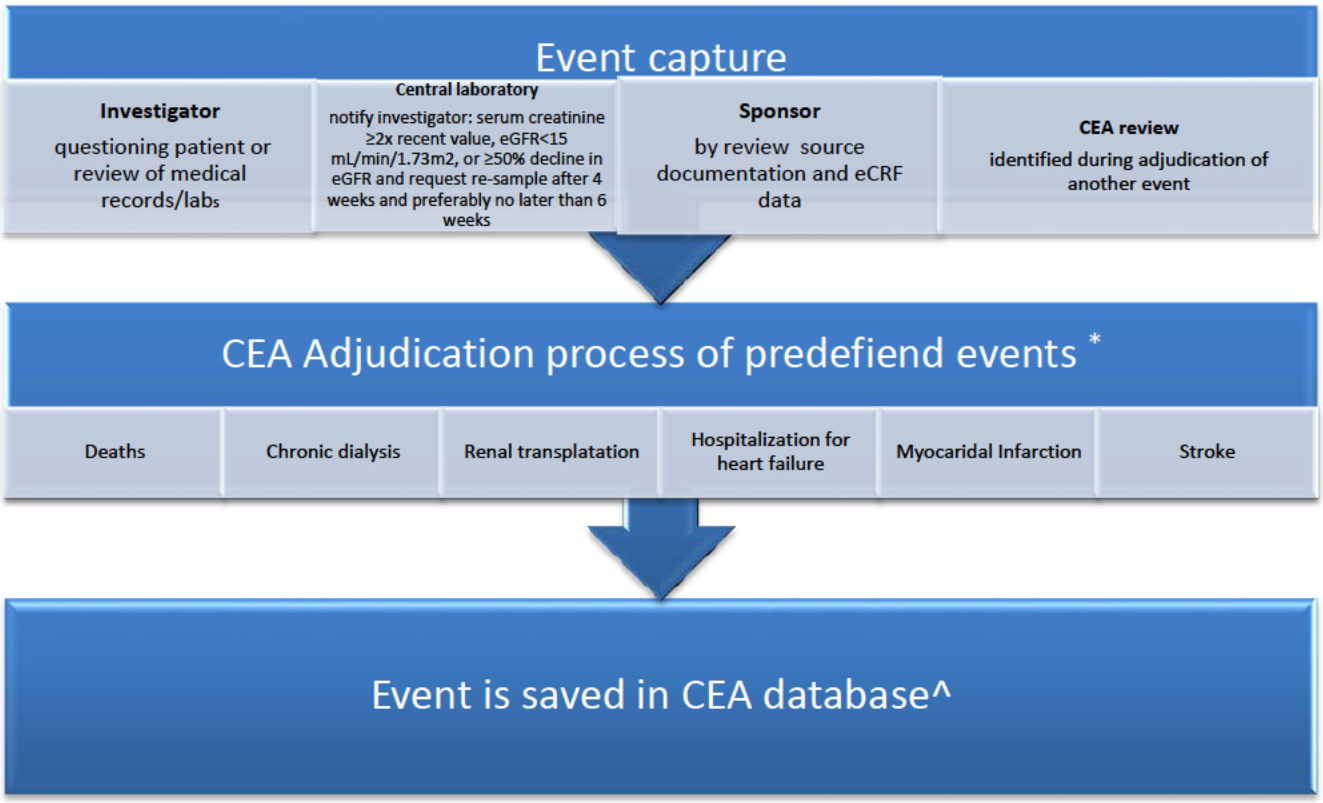
SAP: statistical analysis plan; EC: Executive Committee; CEA: Clinical Event Adjudication; DMC: Data Monitoring Committee; NLC: National Leaders Committee
^Study stop was recommended by the DMC during a regular review meeting to assess data (February 26, 2020 data extraction)
*On January 8,2021, the Sponsor provided V1 of the CEA as part of an FDA information request

Table 44 Summary of administrative discussions related to the interim analysis and decision to stop the trial

(b) (4)

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Figure 21. Capture of events of interest in DAPA-CKD



*2 physician reviewers review each event. For stroke events at least on CEA physician should be a neurologist; for renal events, at least one CEA reviewer should be a nephrologist; for HF and MI events at least one CEA reviewer should be a cardiologist.
^ complete agreement of the 2 reviewers will result in the capture of the event in the CEA database, if not, then disagreements may be resolved via re-review of the event by at least 3 CEA reviewers (Phase II review) and documented in minutes (for the following reasons: Death-disagreement between CV and non-cardiovascular death/ renal or non-CV death subcategory, disagreements between HF groups or no HF, disagreement between dialysis (yes/no), kidney transplantation (yes/no), doubling of serum creatinine compared to the most recent central laboratory measurement (yes/no), MI (yes/no), stroke (yes/no)) . Minor disagreements refer to other disagreements, which may be resolved by the 2 CEA physician reviewers that previously reviewed the case.

Table 45 Endpoint definitions

	Definition
Renal	
Kidney transplantation (Adjudicated)	Criteria will be met if kidney transplantation is performed. The date of the kidney transplantation will be used to define the date of reaching the endpoint. Patients with peri-operative death at kidney transplantation or kidney transplant organ failure will still be considered as kidney transplantation.
Chronic dialysis (Adjudicated)	Must meet either of these criteria 1) The treatment has been ongoing for at least 28 days. 2) The dialysis treatment was stopped before day 28 due to death, futility or patient electing to stop dialysis AND the renal deterioration is deemed irreversible. The date of the first dialysis treatment will be used to define the event start date. In patients starting dialysis, also the reason for renal failure will be adjudicated as either: 1) acute renal failure or 2) progression of underlying chronic kidney disease
Doubling of serum creatinine as compared to	In patients not receiving dialysis, all events of doubling of serum creatinine, based on a central OR local laboratory result compared to the most recent central laboratory value, will be adjudicated.

the most recent central laboratory results (adjudicated)	The most probable reason for the doubling of serum creatinine will be adjudicated as one of the following: 1) acute deterioration not related to an underlying renal disease (i.e. due to any acute event such as, but not limited to, infection, dehydration, CV event, drugs/toxins) or 2) deterioration related to the underlying renal disease.
Sustained eGFR<15 (**Not** adjudicated)	Criteria is met if there are two consecutive central laboratory eGFR values <15 ml/min/1.73 m^2 at least 28 days a part. The start date of the event is the date of the first central laboratory measurement. If a local laboratory result indicates an eGFR value <15 ml/min/1.73 m^2, the patient should return to site for a central laboratory sampling, followed by a re-sampling after at least 28 days.
Sustained eGFR decline ≥ 50% (**Not** adjudicated)	Criteria is met if there is a sustained eGFR decline of ≥50% from baseline, where sustained is defined as two consecutive central laboratory eGFR values at least 28 days a part. The start date of the event is the date of the first central laboratory measurement. If a local laboratory result indicates an eGFR decline of ≥50% from baseline, the patient should return to site for a central laboratory sampling, followed by a re-sampling after at least 28 days.
Death (classified as CV, non-CV or undetermined cause of death)	
CV death (adjudicated)	Includes the following 7 categories: 1. *Death due to MI* – is defined as death occurring within 30 days after a myocardial infarction or consequences seen after MI (i.e., progressive CHF, refractory arrhythmia). Death may be sudden and unexpected after cardiac event suggesting an MI or may be result from a procedure to treat an MI. 2. *Sudden cardiac death* – includes the following: death witnessed and instantaneous without new or worsening symptoms; death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, death witnessed and attributed to arrhythmia; death after unsuccessful resuscitation from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology; death>24 hours after patient has been successfully resuscitated from cardiac arrest and without identification of non-cardiovascular etiology; or unwitnessed death in a patient seen alive an stable ≤24 hours prior to being found dead without any evidence supporting a specific non-cv death cause. 3. *Death due to heart failure or cardiogenic shock*- death occurring in the context of worsening HF (heart failure) not in the context of acute MI and including any of these criteria: new or worsening sigs of HF requiring intensification/start of heart failure treatment (iv drug therapy or oxygen, bed confinement); pulmonary edema causing tachypnea/distress, cardiogenic shock 4. *Death due to stroke*- cerebrovascular event which leads to death within 30 days 5. *Death due to cardiovascular procedure*- death caused by immediate complications of a cardiovascular procedure 6. *Death due to cardiovascular hemorrhage*- death due to hemorrhage such as non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture or hemorrhage causing cardiac tamponade 7. *Death due to other cardiovascular cause*- cardiovascular death not included in other categories listed above but with known cause (i.e., pulmonary embolus, or peripheral arterial disease)
Non-CV death (adjudicated)	Defined as any death not covered by CV death and falling into the following categories: pulmonary failure, gastrointestinal causes, hepatobiliary, pancreatic, infection (including sepsis), inflammatory (SIRS, anaphylaxis), hemorrhage that is neither CV nor stroke, non-CV procedure or surgery, trauma, suicide, non-prescription/prescription drug reaction or overdose, neurological, malignancy, other. In addition, renal death was included and defined as death due to ESKD, but dialysis treatment was deliberately withheld (dialysis was not started or discontinued) for any reason. E.g. patient refuses

	dialysis, treating physician considers the dialysis futile, or dialysis is not available. If death is related to other causes than ESKD, the death will NOT be adjudicated as renal cause of death.
Undetermined cause of death (adjudicated)	Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death.
Cardiovascular and cerebrovascular definitions	
Hospitalization for heart failure (HF) (adjudicated)	Patient is admitted to the hospital (≥24 hours) with a primary diagnosis of HF due to at least 1 heart failure symptom (i.e., dyspnea, decreased exercise tolerance, fatigue, other symptoms of end organ perfusion or volume overload), and has objective evidence of new/worsening heart failure (based on at least 2 physical exam findings or 1 physical exam finding and 1 laboratory finding [peripheral edema, ascites, pulmonary findings, JVP, S3 gallop, rapid weight gain due to fluid retention, increases in BNP>500 pg/mL or NT-proBNP>2,000 pg/mL), and radiological evidence of pulmonary congestion, and non-invasive/invasive evidence of elevated left/right ventricular filling pressure), and treatment for HF (including at least one: augmentation of oral diuretic treatment, IV diuretic or vasoactive therapy or mechanical/surgical intervention [i.e., intraaortic balloon pump, ultrafiltration)
Myocardial infarction (adjudicated)	Definition based on the Third Universal Definition (Thygesen et al 2012) criteria. - *Acute MI*- there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia meeting any of the following: o rise/fall of cardiac biomarker (i.e., cardiac troponin with at least 1 value >99th percentile upper limit) and symptoms of ischemia, ST/T wave changes, LBBB, pathological Q waves, loss of myocardium/wall motion abnormality on imaging or identification of thrombus by angiography or autopsy o Cardiac death, PCI-related MI, stent thrombosis associated with MI when detected by coronary angiography/autopsy, or CABG-related MI. Additional criteria for classification of MI and ECG criteria are specified in the Adjudication charter
Stroke	Stroke is defined as an acute episode of neurologic dysfunction attributed to a central nervous system vascular cause and documented by imaging (i.e., CT scan or MRI scan showing area of acute infarction or hemorrhage compatible with the neurologic symptoms) or autopsy. The following 4 criteria must be met : 1. Rapid onset of a focal/global neurological deficit, 2. duration of neurological deficit≥ 24 hours OR <24 hours if pharmacological or nonpharmacologic therapy administered (i.e., thrombolytic, intracranial angioplasty) or if imaging documents new hemorrhage/infarct or deficit result in death, 3. No other non-stroke cause identified, 4. Confirmation of diagnosis by at least one of the following: internal medicine, neurology or neurosurgical specialist, brain imaging, lumbar puncture or autopsy findings. The adjudication charter further specifies classification of stroke (i.e., primary ischemic, primary hemorrhagic, and unknown/no imaging performed)
Source: Reviewer summarized information from the CEA charter dated 14 February 2020	

Figure 22 Sample enrollment form capturing CKD diagnosis

D169AC00001: (b) (4)
Folder: Visit 1 (Enrolment)
Form: CKD Diagnosis (CKDD)
Generated On: (b) (4)

(Version CV16:11 Date: 2016-11-09)

Diagnosis based on kidney biopsy	No ☐
	Yes ■
Most likely etiology of CKD	Diabetic nephropathy ■
	Ischaemic/Hypertensive nephropathy ☐
	Chronic glomerulonephritis ☐
	Renal artery stenosis ☐
	Chronic pyelonephritis (infectious) ☐
	Chronic interstitial nephritis ☐
	Obstructive nephropathy ☐
	Unknown ☐
	Other ☐
Specify Other	
Chronic glomerulonephritis type	IgA nephropathy ☐
	Focal segmental glomerulosclerosis (FSGS) ☐
	Membranous nephropathy ☐
	Minimal change ☐
	Other primary or secondary glomerulonephritis ☐
Specify Other glomerulonephritis	

Source: electronic case report for submitted by Applicant

12.5. Exposure in dialysis patients

DAPA-CKD did not require discontinuation of study drug after initiation of dialysis. A total of 29 patients in the dapagliflozin group and 47 patients in the placebo group received treatment for ≥1 day after starting dialysis. See Table 46 for additional information on duration of treatment after starting dialysis in this subset.

Table 46 Exposure after starting dialysis in patients who initiated dialysis in DAPA-CKD

Parameter	Dapa 10 mg N=29	Placebo N=47
Duration of treatment since dialysis (months)		
Mean (SD)	7.1 (7.3)	6.6 (7.1)
Median (Min, Max)	4.3 (0.03, 25.9)	5.2 (0.03, 28.5)
Patients treated since dialysis, by duration, n (%)		
Any duration* (at least one day)	29 (100)	47 (100)
<1 month	5 (17.2)	13 (27.7)
≥1 month	24 (82.8)	34 (72.3)
≥6 months	11 (37.9)	18 (38.3)
≥12 months	5 (17.2)	8 (17.0)
≥18 months	3 (10.3)	4 (8.5)
≥24 months	2 (6.9)	2 (4.3)
≥28 months	0 (0.0)	2(4.3)

*Duration of treatment (months) since dialysis was calculated by (end of treatment date – start date of dialysis + 1)/30
Source: Reviewer's table, dataset: date

12.6. Subject characteristics

Figure 23 Baseline eGFR by baseline UACR - FAS

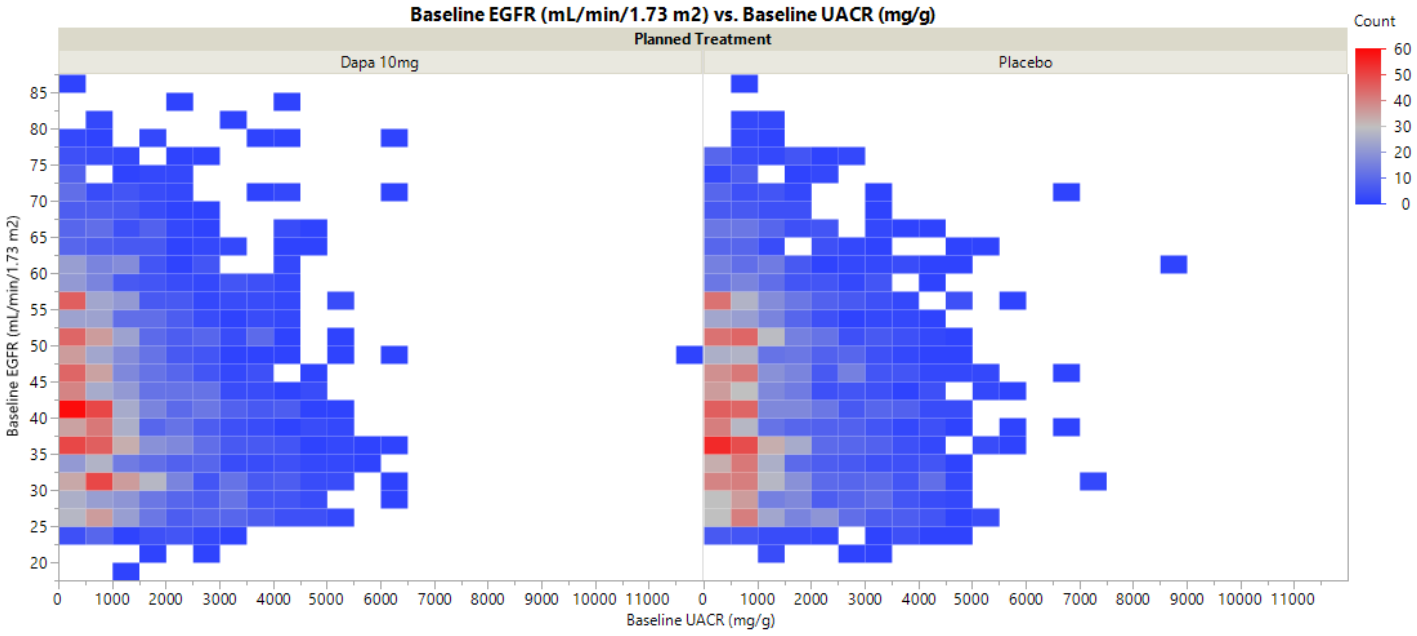
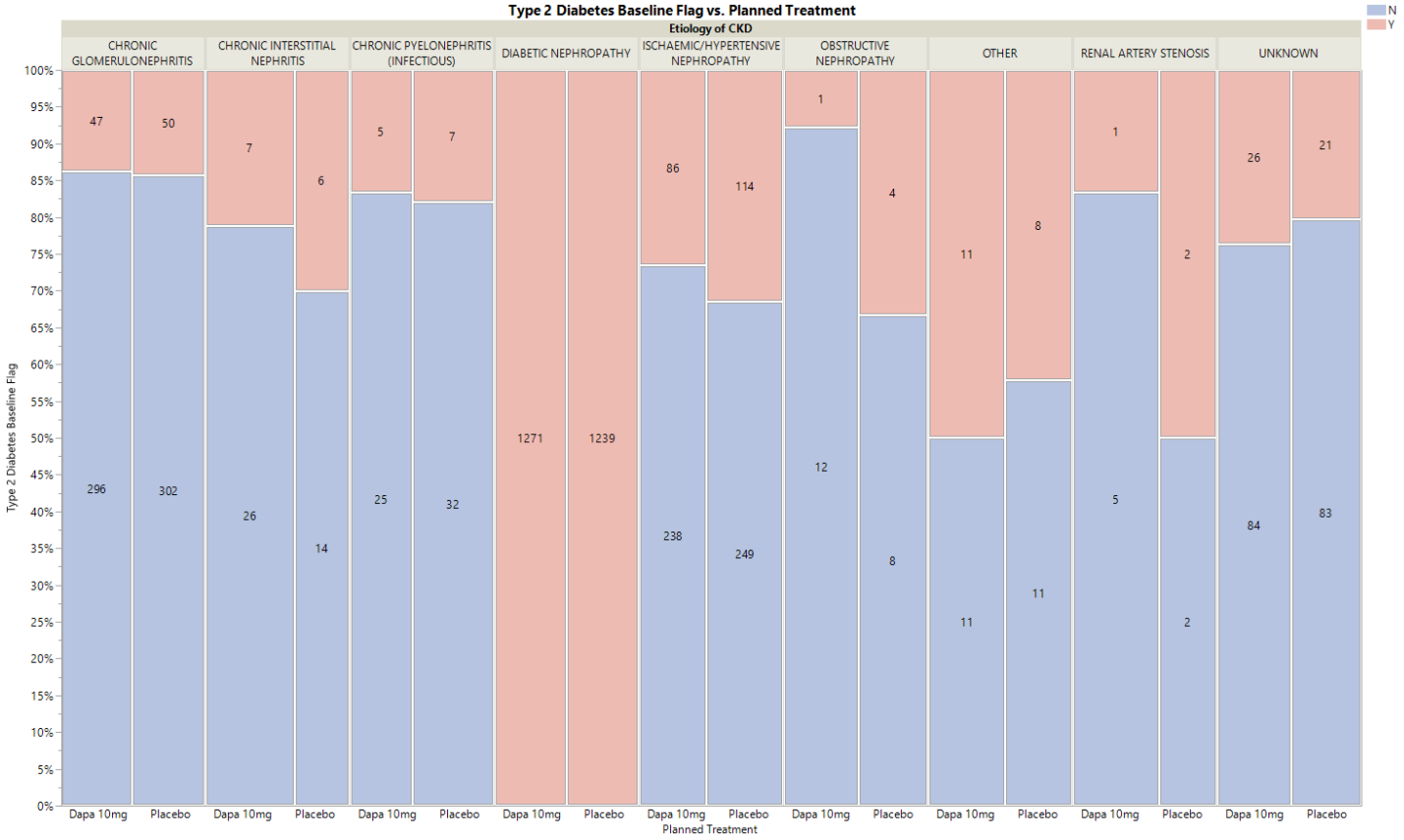
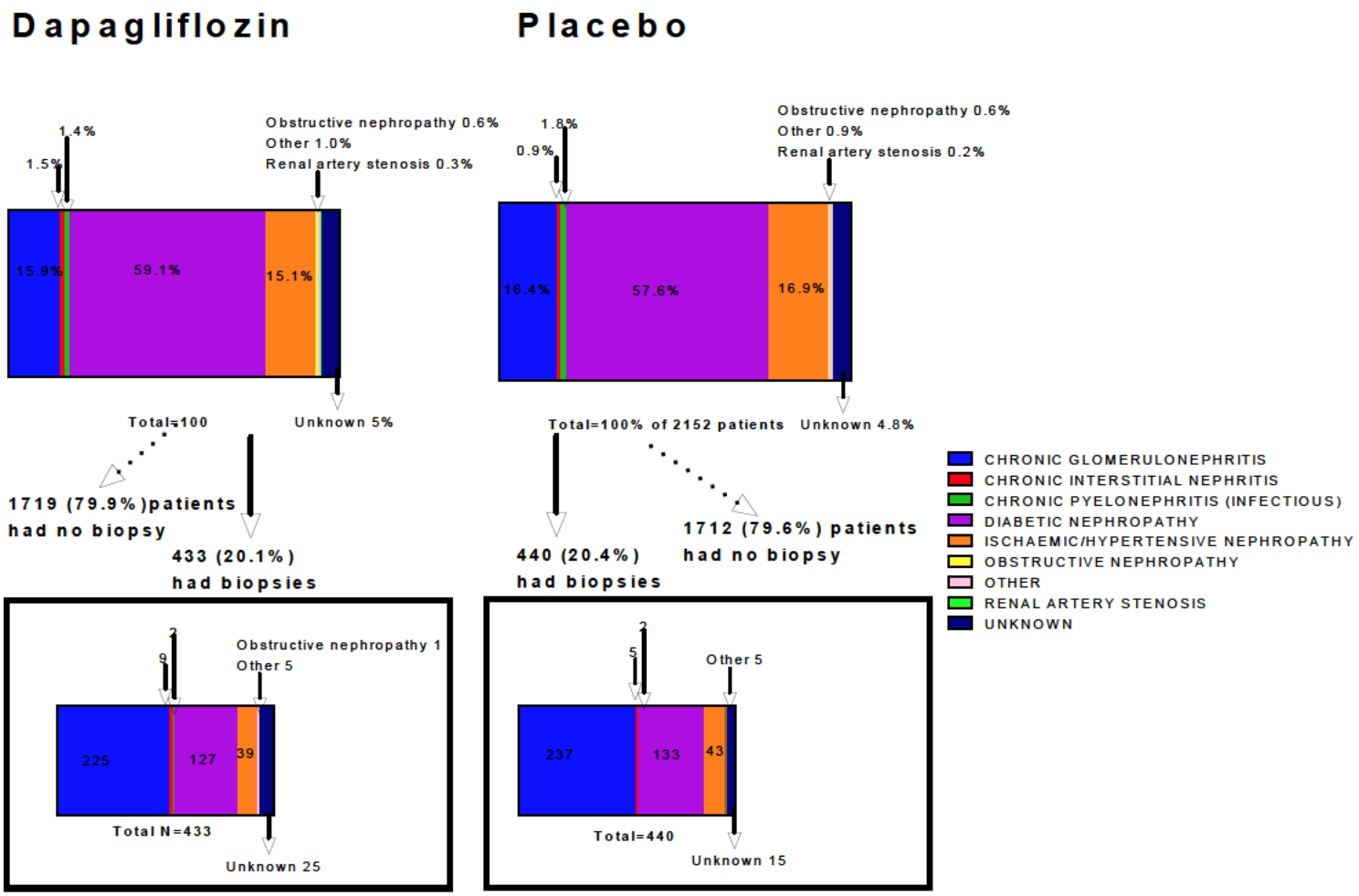


Figure 24 Etiology of CKD in patients with and without T2DM (Y/N) -FAS



Numbers shown in each bar is the subject count
Source: reviewer derived from ADSL.xpt

Figure 25 Chronic kidney disease etiology (all patients and biopsy-confirmed)-FAS



Source: reviewer generated from ADSL.xpt and FA.xpt datasets

Table 47 Diagnosis based on kidney biopsy by CKD etiologies (FAS)

	Dapa 10 mg (N = 2152)		Placebo (N = 2152)		Total (N = 4304)	
Subject characteristic Category	Number of subjects	Subjects with biopsy n (%)	Number of subjects	Subjects with biopsy n (%)	Number of subjects	Subjects with biopsy n (%)
CKD etiology n (%)						
Diabetic Nephropathy	1271	127 (10.0)	1239	133 (10.7)	2510	260 (10.4)
Ischaemic/Hypertensive Nephropathy	324	39 (12.0)	363	43 (11.8)	687	82 (11.9)
Chronic Glomerulonephritis	343	225 (65.6)	352	237 (67.3)	695	462 (66.5)
FSGS	53	45 (84.9)	62	59 (95.2)	115	104 (90.4)
IgA Nephropathy	137	129 (94.2)	133	125 (94.0)	270	254 (94.1)
Membranous Nephropathy	19	16 (84.2)	24	22 (91.7)	43	38 (88.4)
Minimal Change	7	6 (85.7)	4	3 (75.0)	11	9 (81.8)
Other Glomerulonephritis	127	29 (22.8)	129	28 (21.7)	256	57 (22.3)
Chronic Interstitial Nephritis	33	9 (27.3)	20	5 (25.0)	53	14 (26.4)
Chronic Pyelonephritis (Infectious)	30	2 (6.7)	39	2 (5.1)	69	4 (5.8)
Obstructive Nephropathy	13	1 (7.7)	12	0	25	1 (4.0)
Renal Artery Stenosis	6	0	4	0	10	0
Unknown	110	25 (22.7)	104	15 (14.4)	214	40 (18.7)
Other	22	5 (22.7)	19	5 (26.3)	41	10 (24.4)
Total	2152	433 (20.1)	2152	440 (20.4)	4304	873 (20.3)

Dapa, dapagliflozin; FAS, full analysis set; FSGS, focal segmental glomerulosclerosis; Ig, immunoglobulin; N, number of subject in treatment group; Other Glomerulonephritis, other primary or secondary glomerulonephritis.

Source: Information Request provided by Applicant on January 22, 2021

Table 48 Summary of the CKD etiology category "other"

Category	Number of patients (N = 41)
Unclear etiology	13
Mixed diabetes and other conditions	9
Not specified[a]	4
Tubulointerstitial nephritis	8
Drug related	2
Gout nephropathy	1
Lithiasis/calcinosis	4
Reflux nephropathy	1
Unspecified disease in single kidney	7
AKI	4
Cystic disease	2
Glomerular diseases	3
Amyloidosis	1
IgA nephropathy	1
IgA vasculitis	1
Hepatorenal syndrome	1
Hereditary nephropathy	3
Fabry's disease	2
Hereditary nephropathy, not specified	1

[a] Small kidneys, hypertension, mixed etiology
AKI, acute kidney injury; Ig, immunoglobulin; N, number of subjects
Source: Information Request provided by Applicant on January 22, 2021

Table 49 Summary of the CKD etiology category "other glomerulonephritis"

Category	Number of patients (N = 256)
No specified type of glomerulonephritis	214
Immunoglobulin and complement-mediated	25
C3 glomerulonephritis	2
Deposition disease	1
IgA vasculitis	1
IgM nephropathy	1
Lupus nephritis	1
Membranoproliferative	10
Mesangioproliferative	9
Infection related glomerulonephritis	7
Alport Disease	6
Amyloidosis	2
Thrombotic microangiopathies	2

Information Request provided by Applicant on January 22, 2021

Table 50 Demographic Characteristics-Chronic Glomerulonephritis

	Dapagliflozin 10 mg N=343	Placebo N=352	All N=695
Age, Mean (SD), years	51.9 (13.6)	51.7 (13.9)	51.8 (13.8)
Female sex; N (%)	117 (34.1)	137 (38.9)	254 (36.5)
Race; N (%)			
White	165 (48.1)	176 (50)	341 (49.1)
Asian	162 (47.2)	164 (46.6)	326 (46.9)
Other	4 (1.2)	6 (1.7)	10 (1.4)
American Indian/Alaska Native	6 (1.7)	3 (0.9)	9 (1.3)
Black/African American	6 (1.7)	3 (0.9)	9 (1.3)
Ethnicity			
Hispanic or Latino, N (%)	37 (10.8)	36 (10.2)	73 (10.5)
Geographic Region; N (%)			
Asia	149 (43.4)	150 (42.6)	299 (43)
Europe	121 (35.3)	121 (34.4)	242 (34.8)
North America	39 (11.4)	49 (13.9)	88 (12.7)
Latin/South America	34 (9.9)	32 (9.1)	66 (9.5)
T2DM at Baseline, N (%)	47 (13.7)	50 (14.2)	97 (14)
Baseline UACR; mean (SD)	1235.7 (911.6)	1363.2 (1081.5)	1300.3 (1002.6)
Baseline eGFR (mL/min/1.73 m^2); mean (SD)	42.9 (11.9)	42.8 (11.9)	42.8 (11.9)
eGFR (mL/min/1.73 m^2); categories			
< 30	44 (12.8)	53 (15.1)	97 (14)
30 and < 45	158 (46.1)	151 (42.9)	309 (44.5)
45 and < 60	106 (30.9)	117 (33.2)	223 (32.1)
≥ 60	35 (10.2)	31 (8.8)	66 (9.5)

Source: ADSL.xpt dataset

Table 51 Demographic Characteristics-Diabetic Nephropathy

	Dapagliflozin 10 mg N=1271	Placebo N=1239	All N=2510
Age, Mean (SD), years	64.2 (9.7)	65 (9.4)	64.6 (9.6)
Female sex; N (%)	435 (34.2)	409 (33)	844 (33.6)
Race; N (%)			
White	657 (51.7)	676 (54.6)	1333 (53.1)
Asian	409 (32.2)	373 (30.1)	782 (31.2)
Other	88 (6.9)	84 (6.8)	172 (6.9)
Black/African American	66 (5.2)	49 (4)	115 (4.6)
American Indian/Alaska Native	51 (4)	56 (4.5)	107 (4.3)
Native Hawaiian/Pacific Islander	0 (0)	1 (0.1)	1 (0)
Ethnicity			
Hispanic or Latino, N (%)	374 (29.4)	361 (29.1)	735 (29.3)
Geographic Region; N (%)			
Asia	374 (29.4)	331 (26.7)	705 (28.1)
Europe	307 (24.2)	335 (27)	642 (25.6)
Latin/South America	322 (25.3)	299 (24.1)	621 (24.7)
North America	268 (21.1)	274 (22.1)	542 (21.6)
T2DM at Baseline, N (%)	1271 (100)	1239 (100)	2510 (100)

Baseline UACR; mean (SD)	1517.7 (1329.3)	1480.7 (1264.7)	1499.4 (1297.7)
Baseline eGFR (mL/min/1.73 m^2); mean (SD)	44.2 (12.7)	43.5 (12.4)	43.8 (12.6)
eGFR (mL/min/1.73 m^2); categories			
< 30	162 (12.7)	176 (14.2)	338 (13.5)
30 and < 45	560 (44.1)	520 (42)	1080 (43)
45 and < 60	384 (30.2)	406 (32.8)	790 (31.5)
≥ 60	165 (13)	137 (11.1)	302 (12)

Source: ADSL.xpt dataset

Table 52 Demographic Characteristics- Ischemic/hypertensive nephropathy

	Dapagliflozin 10 mg N=324	**Placebo N=363**	**All N=687**
Age, Mean (SD), years	64.2 (12.1)	63.1 (11.9)	63.6 (12)
Female sex; N (%)	87 (26.9)	100 (27.5)	187 (27.2)
Race; N (%)			
White	177 (54.6)	198 (54.5)	375 (54.6)
Asian	104 (32.1)	109 (30)	213 (31)
Other	25 (7.7)	29 (8)	54 (7.9)
Black/African American	14 (4.3)	12 (3.3)	26 (3.8)
American Indian/Alaska Native	3 (0.9)	15 (4.1)	18 (2.6)
Native Hawaiian/Pacific Islander	1 (0.3)	0 (0)	1 (0.1)
Ethnicity			
Hispanic or Latino, N (%)	71 (21.9)	121 (33.3)	192 (27.9)
Geographic Region; N (%)			
Asia	98 (30.2)	103 (28.4)	201 (29.3)
Europe	96 (29.6)	88 (24.2)	184 (26.8)
Latin/South America	61 (18.8)	105 (28.9)	166 (24.2)
North America	69 (21.3)	67 (18.5)	136 (19.8)
T2DM at Baseline, N (%)	86 (26.5)	114 (31.4)	200 (29.1)
Baseline UACR; mean (SD)	1106.2 (973.6)	1032.2 (916.2)	1067.1 (943.8)
Baseline eGFR (mL/min/1.73 m^2); mean (SD)	42 (11.2)	42 (12.6)	42 (12)
eGFR (mL/min/1.73 m^2); categories			
< 30	47 (14.5)	63 (17.4)	110 (16)
30 and < 45	156 (48.1)	166 (45.7)	322 (46.9)
45 and < 60	99 (30.6)	104 (28.7)	203 (29.5)
≥ 60	22 (6.8)	30 (8.3)	52 (7.6)

Source: ADSL.xpt dataset

12.7. Selective narratives for efficacy endpoints

Review of selected ≥ 50% eGFR decline events

Subject identifier (b) (6) 74-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline eGFR	Percent change from baseline
	44	mL/min/1.73 m2	44	
-21	24	mL/min/1.73 m2	44	
-10	48	mL/min/1.73 m2	44	
-2	44	mL/min/1.73 m2	44	
6	43	mL/min/1.73 m2	44	-2.272727273
14	48	mL/min/1.73 m2	44	9.090909091
62	20	mL/min/1.73 m2	44	-54.54545455
114	22	mL/min/1.73 m2	44	-50
243	19	mL/min/1.73 m2	44	-56.81818182
357	16	mL/min/1.73 m2	44	-63.63636364
469	14	mL/min/1.73 m2	44	-68.18181818
498	16	mL/min/1.73 m2	44	-63.63636364
587	17	mL/min/1.73 m2	44	-61.36363636
708	17	mL/min/1.73 m2	44	-61.36363636
827	9	mL/min/1.73 m2	44	-79.54545455
918	9	mL/min/1.73 m2	44	-79.54545455
964	8	mL/min/1.73 m2	44	-81.81818182
1034	5	mL/min/1.73 m2	44	-88.63636364

Subject identifier (b) (6): 46-year-old woman randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline eGFR	Percent change from baseline
	39	mL/min/1.73 m2	39	
-7	39	mL/min/1.73 m2	39	
1	39	mL/min/1.73 m2	39	
14	34	mL/min/1.73 m2	39	-12.82051282
64	39	mL/min/1.73 m2	39	0
126	40	mL/min/1.73 m2	39	2.564102564
232	30	mL/min/1.73 m2	39	-23.07692308
372	20	mL/min/1.73 m2	39	-48.71794872
414	23	mL/min/1.73 m2	39	-41.02564103
470	21	mL/min/1.73 m2	39	-46.15384615
512	21	mL/min/1.73 m2	39	-46.15384615
609	15	mL/min/1.73 m2	39	-61.53846154
684	13	mL/min/1.73 m2	39	-66.66666667
733	13	mL/min/1.73 m2	39	-66.66666667
784	11	mL/min/1.73 m2	39	-71.79487179
845	7	mL/min/1.73 m2	39	-82.05128205

Subject identifier [redacted] (b) (6): 27-year-old female randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline eGFR	Percent change from baseline
	31	mL/min/1.73 m2	31	
-7	33	mL/min/1.73 m2	31	
1	29	mL/min/1.73 m2	31	
15	32	mL/min/1.73 m2	31	3.225806452
63	30	mL/min/1.73 m2	31	-3.225806452
121	27	mL/min/1.73 m2	31	-12.90322581
241	18	mL/min/1.73 m2	31	-41.93548387
361	5	mL/min/1.73 m2	31	-83.87096774
494	4	mL/min/1.73 m2	31	-87.09677419

Subject identifier [redacted] (b) (6): 73-year-old man randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline eGFR	Percent change from baseline
	50	mL/min/1.73 m2	50	
-14	54	mL/min/1.73 m2	50	
1	46	mL/min/1.73 m2	50	
15	57	mL/min/1.73 m2	50	14
75	53	mL/min/1.73 m2	50	6
126	58	mL/min/1.73 m2	50	16
231	50	mL/min/1.73 m2	50	0
357	43	mL/min/1.73 m2	50	-14
511	30	mL/min/1.73 m2	50	-40
609	22	mL/min/1.73 m2	50	-56
649	24	mL/min/1.73 m2	50	-52

Subject identifier [redacted] (b) (6): 69-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	Percent change from baseline
	31	mL/min/1.73 m2	31	
-13	31	mL/min/1.73 m2	31	
1	30	mL/min/1.73 m2	31	
14	25	mL/min/1.73 m2	31	-19.35483871
63	27	mL/min/1.73 m2	31	-12.90322581
121	23	mL/min/1.73 m2	31	-25.80645161
241	19	mL/min/1.73 m2	31	-38.70967742
360	18	mL/min/1.73 m2	31	-41.93548387
493	21	mL/min/1.73 m2	31	-32.25806452
605	19	mL/min/1.73 m2	31	-38.70967742
729	19	mL/min/1.73 m2	31	-38.70967742
841	14	mL/min/1.73 m2	31	-54.83870968
875	11	mL/min/1.73 m2	31	-64.51612903

Subject identifier (b) (6) 50-year-old female randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	Percent change from baseline
	32	mL/min/1.73 m2	32	
-11	33	mL/min/1.73 m2	32	
1	30	mL/min/1.73 m2	32	
16	30	mL/min/1.73 m2	32	-6.25
64	33	mL/min/1.73 m2	32	3.125
120	31	mL/min/1.73 m2	32	-3.125
254	34	mL/min/1.73 m2	32	6.25
379	35	mL/min/1.73 m2	32	9.375
493	24	mL/min/1.73 m2	32	-25
611	11	mL/min/1.73 m2	32	-65.625
646	13	mL/min/1.73 m2	32	-59.375
731	10	mL/min/1.73 m2	32	-68.75
855	4	mL/min/1.73 m2	32	-87.5

Subject identifier (b) (6): 64-year-old female randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	Percent change from baseline
	60	mL/min/1.73 m2	60	
-8	59	mL/min/1.73 m2	60	
1	61	mL/min/1.73 m2	60	
18	44	mL/min/1.73 m2	60	-26.66666667
68	47	mL/min/1.73 m2	60	-21.66666667
127	20	mL/min/1.73 m2	60	-66.66666667
253	43	mL/min/1.73 m2	60	-28.33333333
372	42	mL/min/1.73 m2	60	-30
487	38	mL/min/1.73 m2	60	-36.66666667
602	29	mL/min/1.73 m2	60	-51.66666667
666	25	mL/min/1.73 m2	60	-58.33333333
725	19	mL/min/1.73 m2	60	-68.33333333
876	10	mL/min/1.73 m2	60	-83.33333333

Subject identifier (b) (6): 52-year-old male randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	Percent change from baseline
	58	mL/min/1.73 m2	58	
-21	23	mL/min/1.73 m2	58	
-15	59	mL/min/1.73 m2	58	
1	56	mL/min/1.73 m2	58	
15	23	mL/min/1.73 m2	58	-60.34482759
62	21	mL/min/1.73 m2	58	-63.79310345
120	18	mL/min/1.73 m2	58	-68.96551724
150	17	mL/min/1.73 m2	58	-70.68965517
239	17	mL/min/1.73 m2	58	-70.68965517
265	12	mL/min/1.73 m2	58	-79.31034483
351	17	mL/min/1.73 m2	58	-70.68965517
470	11	mL/min/1.73 m2	58	-81.03448276
589	9	mL/min/1.73 m2	58	-84.48275862
710	11	mL/min/1.73 m2	58	-81.03448276
829	9	mL/min/1.73 m2	58	-84.48275862
962	11	mL/min/1.73 m2	58	-81.03448276
1036	9	mL/min/1.73 m2	58	-84.48275862

Subject identifier (b) (6) 61-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	Percent change from baseline
	62	mL/min/1.73 m2	62	
-14	56	mL/min/1.73 m2	62	
1	67	mL/min/1.73 m2	62	
22	61	mL/min/1.73 m2	62	-1.612903226
96	59	mL/min/1.73 m2	62	-4.838709677
127	62	mL/min/1.73 m2	62	0
246	49	mL/min/1.73 m2	62	-20.96774194
362	47	mL/min/1.73 m2	62	-24.19354839
491	37	mL/min/1.73 m2	62	-40.32258065
624	25	mL/min/1.73 m2	62	-59.67741935
679	26	mL/min/1.73 m2	62	-58.06451613
788	25	mL/min/1.73 m2	62	-59.67741935
861	25	mL/min/1.73 m2	62	-59.67741935
981	19	mL/min/1.73 m2	62	-69.35483871

Subject identifier (b) (6): 60-year-old female randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	Percent change from baseline
	36	mL/min/1.73 m2	36	
-5	35	mL/min/1.73 m2	36	
1	37	mL/min/1.73 m2	36	
15	41	mL/min/1.73 m2	36	13.88888889
58	36	mL/min/1.73 m2	36	0
122	32	mL/min/1.73 m2	36	-11.11111111
234	18	mL/min/1.73 m2	36	-50
260	24	mL/min/1.73 m2	36	-33.33333333
373	14	mL/min/1.73 m2	36	-61.11111111
395	14	mL/min/1.73 m2	36	-61.11111111
409	15	mL/min/1.73 m2	36	-58.33333333
471	10	mL/min/1.73 m2	36	-72.22222222

Review of selected ESKD events

Chronic dialysis:

Subject identifier (b) (6): 48-year-old female randomized to dapagliflozin who had a history of CKD due to diabetic nephropathy, coronary artery disease, hypertension, and T2DM. On study day 855 ((b) (6)), the patient was hospitalized for insertion of a peritoneal dialysis catheter; her eGFR at the time was 7.1 mL/min/1.73m^2. On study day 856, the patient started peritoneal dialysis. During the adjudication process, the site was queried as to whether dialysis was ongoing, and, on (b) (6), the site confirmed that the dialysis was ongoing.

Subject identifier (b) (6) 67-year-old male randomized to dapagliflozin who had a history of CKD, dyslipidemia, hypertension, and T2DM. On study day 660 ((b) (6)) during an admission for a myocardial infarction treated with a drug eluting stent, the patient was transferred to the nephrology team for insertion of a peritoneal dialysis catheter; the patient's eGFR before admission was 13 mL/min/1.73 m^2. The patient was again hospitalized on study day 707 ((b) (6) due to poor drainage of the catheter. Per the narrative, "non-invasive permeabilization maneuvers are continued, achieving functionality" of the catheter, and the patient was discharged with treatment of a peritoneal infection. The site also confirmed dialysis was ongoing on (b) (6) during the adjudication process.

Subject identifier (b) (6): 76-year-old female randomized to dapagliflozin who had a history of CKD, dyslipidemia, hypertension, neuropathy, osteoporosis, and T2DM. On study day 856 (b) (6)), the patient was hospitalized for pneumonia. During the hospitalization, she was found to be acidotic with respiratory distress and lower extremity edema. Laboratories at admission reveal creatinine of 340.5 µmol/L (3.85 mg/dL). Chest x-ray revealed consolidation in the bilateral bases. She was treated with antibiotics and nitroglycerin but developed wheezing and tachypnea. The patient had a femoral catheter inserted and underwent hemodialysis a day later (study day 857). The patient became oliguric and, although dialysis temporarily ameliorated the dyspnea, the patient's oxygen requirements continued to increase. She was

transferred to the ICU and required mechanical intubation. After a discussion with the medical staff, the patient's relatives requested to bring the patient home, and the patient expired. There is no death certificate available. Review of the eGFR trends from enrollment on (b) (6) to (b) (6) revealed a steady decline in eGFR values (from a baseline of 40 to 14 mL/min/1.73 m^2).

Reviewer's comment: This event suggests the patient had an episode of acute on chronic kidney failure that resulted in fluid overload and required dialysis. Per the CEA charter, the event meets the definition of chronic dialysis, because dialysis was stopped due to death, and the kidney failure was likely irreversible given the overall eGFR trend and severity of the event.

Subject identifier (b) (6)*:* 49-year-old male randomized to dapagliflozin who had a history of CKD, hypertension, and dyslipidemia. On study day 343 ((b) (6)), the patient underwent a kidney biopsy to evaluate worsening kidney function with an eGFR at that time of 13.6 mL/min/1.73 m^2. The kidney biopsy reportedly showed a pauci-immune glomerulopathy with mesangial expansion and segmental glomerular sclerosis. On study day 504 ((b) (6)), the patient started dialysis. On study day 814 ((b) (6)), the patient was sent from the peritoneal dialysis outpatient clinic to the emergency department for a diagnosis of peritonitis. The site also confirmed dialysis was ongoing on (b) (6) during the adjudication process.

Subject identifier (b) (6)*:* 73-year-old male randomized to placebo who had a history of CKD, coronary artery bypass, dyslipidemia, hypertension, and T2DM. On study day 841 ((b) (6)), the patient was sent to the emergency department by his nephrologist after noting that his creatinine had increased from a baseline of 3 mg/dL to 6 mg/dL with a potassium of 5.1 mEq/L. The patient reported symptoms of generalized weakness and leg cramps. He had a tunneled dialysis catheter placed on (b) (6) and initiated dialysis on study day 843 ((b) (6)). The investigator confirmed via the eCRF that dialysis was ongoing after 90 days.

eGFR<15 mL/min/1.73m²:

Subject identifier (b) (6): 61-year-old female randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	38	mL/min/1.73 m2	38	
-23	39	mL/min/1.73 m2	38	
-6	38	mL/min/1.73 m2	38	
1	37	mL/min/1.73 m2	38	
15	31	mL/min/1.73 m2	38	
62	36	mL/min/1.73 m2	38	
128	27	mL/min/1.73 m2	38	
230	37	mL/min/1.73 m2	38	
349	27	mL/min/1.73 m2	38	
468	22	mL/min/1.73 m2	38	
589	16	mL/min/1.73 m2	38	
632	13	mL/min/1.73 m2	38	eGFR < 15
727	14	mL/min/1.73 m2	38	eGFR < 15
905	9	mL/min/1.73 m2	38	eGFR < 15

Subject identifier (b) (6): 59-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	27	mL/min/1.73 m2	27	
-16	30	mL/min/1.73 m2	27	
1	23	mL/min/1.73 m2	27	
13	23	mL/min/1.73 m2	27	
55	26	mL/min/1.73 m2	27	
126	19	mL/min/1.73 m2	27	
233	21	mL/min/1.73 m2	27	
357	18	mL/min/1.73 m2	27	
468	14	mL/min/1.73 m2	27	eGFR < 15
524	14	mL/min/1.73 m2	27	eGFR < 15
565	15	mL/min/1.73 m2	27	
588	14	mL/min/1.73 m2	27	eGFR < 15
653	13	mL/min/1.73 m2	27	eGFR < 15
707	11	mL/min/1.73 m2	27	eGFR < 15
726	10	mL/min/1.73 m2	27	eGFR < 15
772	12	mL/min/1.73 m2	27	eGFR < 15
833	11	mL/min/1.73 m2	27	eGFR < 15
979	7	mL/min/1.73 m2	27	eGFR < 15

Subject identifier (b) (6) 33-year-old male randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	45	mL/min/1.73 m2	45	
-7	47	mL/min/1.73 m2	45	
1	43	mL/min/1.73 m2	45	
15	43	mL/min/1.73 m2	45	
64	40	mL/min/1.73 m2	45	
120	34	mL/min/1.73 m2	45	
239	24	mL/min/1.73 m2	45	
338	12	mL/min/1.73 m2	45	eGFR < 15
365	10	mL/min/1.73 m2	45	eGFR < 15
472	9	mL/min/1.73 m2	45	eGFR < 15
653	4	mL/min/1.73 m2	45	eGFR < 15

Subject identifier (b) (6): 40-year-old female randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	36	mL/min/1.73 m2	36	
-64	42	mL/min/1.73 m2	36	
-21	39	mL/min/1.73 m2	36	
1	32	mL/min/1.73 m2	36	
15	33	mL/min/1.73 m2	36	
63	36	mL/min/1.73 m2	36	
113	27	mL/min/1.73 m2	36	
257	34	mL/min/1.73 m2	36	
358	37	mL/min/1.73 m2	36	
481	34	mL/min/1.73 m2	36	
607	18	mL/min/1.73 m2	36	
656	20	mL/min/1.73 m2	36	
708	14	mL/min/1.73 m2	36	eGFR < 15
730	14	mL/min/1.73 m2	36	eGFR < 15
847	8	mL/min/1.73 m2	36	eGFR < 15
940	9	mL/min/1.73 m2	36	eGFR < 15

Subject identifier (b) (6): 70-year-old male randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	26	mL/min/1.73 m2	26	
-14	26	mL/min/1.73 m2	26	
1	25	mL/min/1.73 m2	26	
15	23	mL/min/1.73 m2	26	
64	29	mL/min/1.73 m2	26	
120	27	mL/min/1.73 m2	26	
232	24	mL/min/1.73 m2	26	
358	21	mL/min/1.73 m2	26	
487	13	mL/min/1.73 m2	26	eGFR < 15
491	12	mL/min/1.73 m2	26	eGFR < 15
502	15	mL/min/1.73 m2	26	
523	16	mL/min/1.73 m2	26	
606	14	mL/min/1.73 m2	26	eGFR < 15
641	14	mL/min/1.73 m2	26	eGFR < 15
669	13	mL/min/1.73 m2	26	eGFR < 15
719	13	mL/min/1.73 m2	26	eGFR < 15

Subject identifier (b) (6): 64-year-old male randomized to placebo with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	34	mL/min/1.73 m2	34	
-14	33	mL/min/1.73 m2	34	
-6	35	mL/min/1.73 m2	34	
1	33	mL/min/1.73 m2	34	
16	36	mL/min/1.73 m2	34	
56	25	mL/min/1.73 m2	34	
126	21	mL/min/1.73 m2	34	
246	12	mL/min/1.73 m2	34	eGFR < 15
280	12	mL/min/1.73 m2	34	eGFR < 15
365	9	mL/min/1.73 m2	34	eGFR < 15
477	12	mL/min/1.73 m2	34	eGFR < 15
603	13	mL/min/1.73 m2	34	eGFR < 15
673	9	mL/min/1.73 m2	34	eGFR < 15

Subject identifier (b) (6): 45-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	26	mL/min/1.73 m2	26	
-9	27	mL/min/1.73 m2	26	
1	25	mL/min/1.73 m2	26	
22	18	mL/min/1.73 m2	26	
135	8	mL/min/1.73 m2	26	eGFR < 15
173	6	mL/min/1.73 m2	26	eGFR < 15

Subject identifier (b) (6): 37-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	38	mL/min/1.73 m2	38	
-14	39	mL/min/1.73 m2	38	
1	36	mL/min/1.73 m2	38	
15	40	mL/min/1.73 m2	38	
29	32	mL/min/1.73 m2	38	
64	32	mL/min/1.73 m2	38	
120	35	mL/min/1.73 m2	38	
232	36	mL/min/1.73 m2	38	
351	24	mL/min/1.73 m2	38	
491	17	mL/min/1.73 m2	38	
526	16	mL/min/1.73 m2	38	
554	17	mL/min/1.73 m2	38	
603	12	mL/min/1.73 m2	38	eGFR < 15
638	11	mL/min/1.73 m2	38	eGFR < 15

Subject identifier (b) (6): 54-year-old male randomized to dapagliflozin with the following eGFR values during the trial:

Study day	eGFR value		Baseline value	flag
	43	mL/min/1.73 m2	43	
-22	46	mL/min/1.73 m2	43	
1	40	mL/min/1.73 m2	43	
15	51	mL/min/1.73 m2	43	
59	42	mL/min/1.73 m2	43	
121	29	mL/min/1.73 m2	43	
245	26	mL/min/1.73 m2	43	
346	22	mL/min/1.73 m2	43	
483	15	mL/min/1.73 m2	43	
543	12	mL/min/1.73 m2	43	eGFR < 15
617	9	mL/min/1.73 m2	43	eGFR < 15
729	7	mL/min/1.73 m2	43	eGFR < 15

Subject identifier (b) (6): 54-year-old female randomized to dapagliflozin with the following eGFR values:

Study day	eGFR value		Baseline value	flag
	28	mL/min/1.73 m2	28	
-9	28	mL/min/1.73 m2	28	
1	28	mL/min/1.73 m2	28	
14	25	mL/min/1.73 m2	28	
84	26	mL/min/1.73 m2	28	
120	24	mL/min/1.73 m2	28	
236	18	mL/min/1.73 m2	28	
357	19	mL/min/1.73 m2	28	
396	17	mL/min/1.73 m2	28	
477	15	mL/min/1.73 m2	28	
593	13	mL/min/1.73 m2	28	eGFR < 15
638	11	mL/min/1.73 m2	28	eGFR < 15
708	10	mL/min/1.73 m2	28	eGFR < 15
852	11	mL/min/1.73 m2	28	eGFR < 15

Kidney transplant:

Subject identifier (b) (6): 30-year-old female randomized to placebo who had a history of hypertension and chronic glomerulonephritis. The patient received a related living donor kidney transplant on (b) (6) The medical record for the hospitalization was included in the adjudication package for the event.

Subject identifier (b) (6): 69-year-old male randomized to placebo who had a history of CKD, dyslipidemia, hypertension, sleep apnea, and T2DM. The patient received a deceased donor kidney transplant on (b) (6)

Renal death:

Subject identifier (b) (6) 59-year-old female randomized to placebo who had history of chronic pyelonephritis, heart failure, and hypertension. On study day 687, the patient developed "end stage kidney disease" with worsening periodic nausea and vomiting. The narrative states that it was "impossible to dialyze the patient," and the patient died. An autopsy was not performed. The death certificate indicates that the primary cause of death was chronic pyelonephritis. The secondary cause of death was "chronic terminal renal failure." No laboratory results are available from around the time of this event; however, the last available eGFR was 4 mL/min/1.73m^2 on study day 605. The event was positively adjudicated as a renal death event.

Subject identifier (b) (6)- 67-year-old male randomized to placebo who had a history of CKD, hypertension, T2DM, dyslipidemia, and neuropathy. On day 327, the patient developed "end stage kidney disease" and was noted to have bilateral crackles, dyspnea on exertion, and bipedal edema. He was admitted to the hospital and received diuresis with clinical improvement. Three days later, he was readmitted with pleural effusions, "underwent 3x a week hemodialysis sessions," the fluid overload improved, and he was discharged. His eGFR around the time dialysis was initiated was 8 mL/min/1.73m^2. He was subsequently hospitalized a month later

for respiratory failure and a catheter-related blood stream infection. He was treated and discharged but refused to continue hemodialysis. He had progressive fatigue and died on day 453 after being found unresponsive by family. The death certificate listed the immediate cause of death as "septic shock," antecedent cause "pneumonia" and "underlying cause as "diabetic nephropathy."

Reviewer's comment: The clinical history leading to the patient's death, and, in particular, his refusal to continue dialysis, supports adjudication of the event as "renal death" as defined in the CEA charter.

Review of selected CV death events
CV death due to MI:

Subject identifier (b) (6): 65-year-old male randomized to dapagliflozin who had a history of chronic interstitial nephritis and hypertension. On study day 155, the patient was found dead by his wife. An autopsy report submitted in the adjudication package listed the cause of death as acute myocardial infarct, coronary occlusion, serious coronary atherosclerosis, serious general atherosclerosis, and cardiomegaly. The report describes that the lumen of the anterior descending branch of the left coronary artery was occluded by a hemorrhaging plaque 2 cm from its origin. The anterior wall of the left ventricle and the interventricular septum showed evidence of acute myocardial infarction. There was also evidence of bilateral ventricular wall thickening.

Subject identifier (b) (6)*:* 51-year-old male randomized to placebo who had a history of CKD, carotid artery stenosis, dyslipidemia, gout, hypertension, and T2DM. On study day 27 (b) (6)), the patient was hospitalized for precordial chest pain and subsequently suffered cardiopulmonary arrest with ventricular tachycardia/ventricular fibrillation storm. An intra-aortic balloon pump was inserted, and he underwent emergent percutaneous coronary intervention. He had an acute stent thrombosis of the left anterior descending artery requiring emergent angioplasty, stent deployment, and thrombus removal. Post-procedure, the patient had evidence of circulatory failure with intestinal necrosis. He was subsequently found to have bilateral pupillary dilation with loss of light reflex, and the patient's family was informed that his brain function was irreversibly impaired. The patient expired. There was no death certificate available.

CV death due to stroke:

Subject identifier (b) (6) 84-year-old male randomized to placebo who had a history of CKD, atrial fibrillation, dyslipidemia, hypertension, peripheral arterial disease, and T2DM. On study 270 ((b) (6)), the patient was seen at his health care center for "language alterations" and was found to be dysarthric. Later that day, the patient presented to the emergency department with worsening dysarthria, a left palsy, and oculocephalic deviation of the right eye. A stroke code was activated. CT of head showed a lobar hematoma. The hospitalization was complicated by a respiratory infection, acute on chronic kidney failure, and hypernatremia. The patient died on study day 277 (b) (6)). There was no death certificate available.

CV death due to sudden cardiac death:

Subject identifier (b) (6) 68-year-old male randomized to placebo with a history of CKD, hypertension, ischemic stroke, myocardial infarction, neuropathy, T2DM, and amputation. The patient's son informed the

investigator that the patient had died suddenly at home. There were no changes to the patient's overall health before his death. The death certificate included in the adjudication package listed the cause of death as acute left ventricle failure, ischemic heart disease, and T2DM.

Subject identifier [redacted]*:* 51-year-old female randomized to placebo with a history of CKD, dyslipidemia, hypertension, neuropathy, peripheral arterial disease, and T2DM. On study day 948 ([redacted]), the patient had symptoms described as "uremia" (anorexia, cognitive deterioration, and lethargy). The patient refused to be admitted to the hospital. On study day 950 ([redacted]), the patient was reported to have suffered an acute myocardial infarction and subsequently died. The death certificate lists the causes of death as acute myocardial infarction, uremia, and terminal chronic kidney disease. There is no further information available.

Review of selected events of hospitalization due to heart failure

Subject identifier [redacted]*:* 56-year-old male randomized to placebo with a history of CKD, peripheral artery disease, hypertension, benign prostatic hypertrophy, requiring indwelling urinary catheter, below the knee amputation, and dilated cardiomyopathy with an ejection fraction of 26%. On study day 154 ([redacted]), the patient was hospitalized with generalized edema, worsening dyspnea, and decreased urination. The presumptive diagnosis was "global decompensated heart failure secondary to progression of underlying disease, exacerbated chronic kidney failure, and hyperkalemia." Hospitalization notes document 3/3 jugular vein engorgement, 2+ edema, and a requirement for non-invasive ventilation. The patient was treated with intravenous loop diuretics and inotropes with adequate diuresis and clinical improvement. The discharge diagnosis was " global heart failure, predominantly on right, secondary to progression of underlying disease. Exacerbation of prerenal CKD due to low flow."

Subject identifier [redacted]*:* 68-year-old male randomized to placebo with a history of CKD, chronic obstructive pulmonary disease, heart failure, hypertension, and T2DM. On study day 603 ([redacted]), the patient was admitted to the hospital with atrial fibrillation and progressively worsening dyspnea at rest. Physical exam findings at admission included bilateral pitting edema. An ECG showed atrial fibrillation with a rate of 76 beats per minute. Chest X-ray was consistent with pulmonary congestion, which improved during hospitalization. A transthoracic echocardiogram showed an ejection fraction of 45.7%. The patient improved with diuretic therapy, and he was discharged on [redacted].

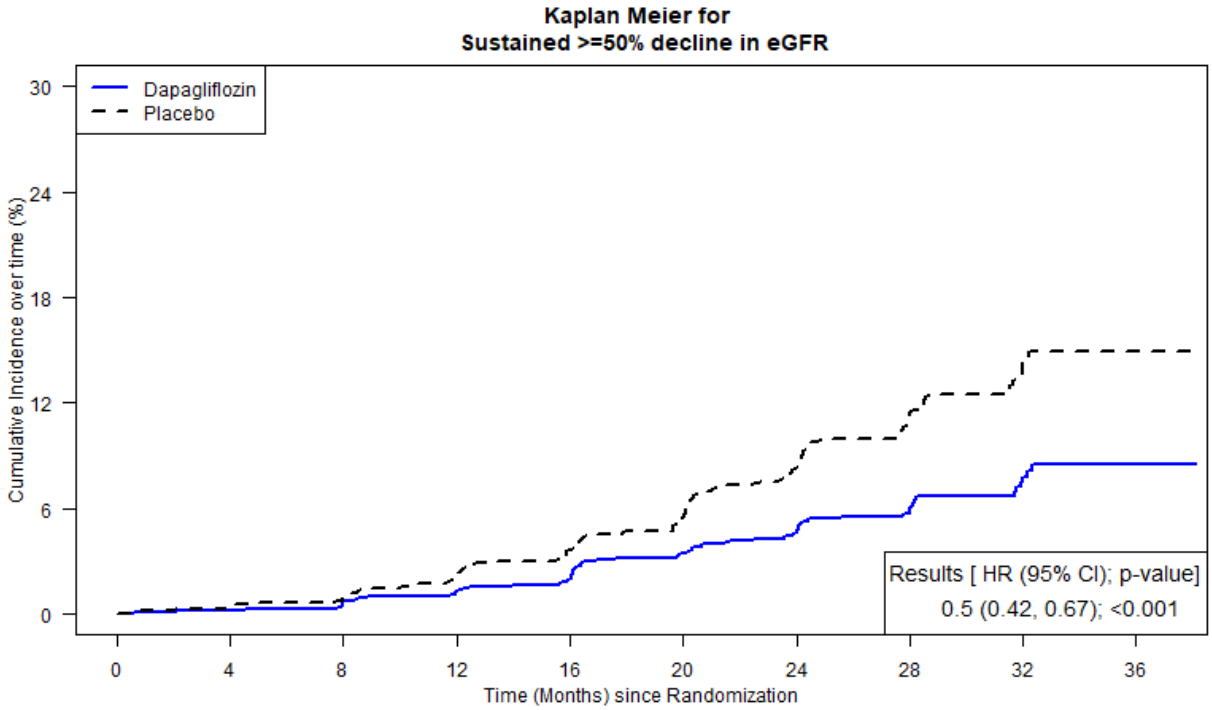
Subject identifier [redacted]*:* 69-year-old male randomized to dapagliflozin with a history of CKD, dyslipidemia, heart failure, hypertension, sleep apnea, and T2DM. On study day 878 ([redacted]), the patient presented to the emergency department with dyspnea and lower extremity edema. The initial diagnosis was volume overload with acute respiratory failure and hypoxia requiring noninvasive ventilation. His NT-proBNP at admission was elevated at 57,347 (reference <899 pg/mL). The patient was started on intravenous furosemide; however, due to progression of renal disease, he was transitioned to dialysis. During the hospitalization, transthoracic and transesophageal echocardiograms revealed moderate to moderately severe aortic regurgitation. After clinical stabilization, he was discharged on [redacted], with plans for aortic valve replacement on a follow up admission.

Subject identifier (b) (6)*:* 66-year-old male randomized to dapagliflozin with a history of CKD, gout, and hypertension. On study day 863 (b) (6)), the patient was admitted to the hospital with progressively worsening dyspnea and lower extremity edema. His BNP on admission was 7,574 (no reference range provided). A transthoracic echocardiogram showed an ejection fraction of 55-60% with moderate concentric left ventricular hypertrophy and grade II diastolic dysfunction. The patient improved with diuresis with intravenous furosemide. He was diagnosed with non-reduced ejection fraction diastolic heart failure and was discharged on (b) (6).

Subject identifier (b) (6)*:* 63-year-old male randomized to dapagliflozin with a history of CKD, atrial fibrillation, coronary artery stenosis, dyslipidemia, hypertension, peripheral artery disease, and T2DM. On study day 561 (b) (6)), the patient was hospitalized with severe left chest pain and shortness of breath, which had persisted for 4 days before admission. The diagnosis at admission was acute myocardial infarction. The patient exhibited orthopnea during the emergency department visit. The ECG on admission was consistent with atrial fibrillation (which was chronic). A transthoracic echocardiogram showed an ejection fraction of 15% (decreased from a prior baseline of 35%). His NT-pro BNP was 18,143 (reference 0-125), and his troponin was 46.19 pg/mL (reference 0-14). The patient underwent coronary angiography, which revealed an 80% stenosis in the beginning portion of the ramus intermedius without other relevant findings. No interventions were conducted as part of the catherization. The patient was admitted to the cardiology service and improved with dobutamine and furosemide. He was discharged on June 29, 2019 with a diagnosis of non-ischemic dilated cardiomyopathy.

12.8. Additional Efficacy Results

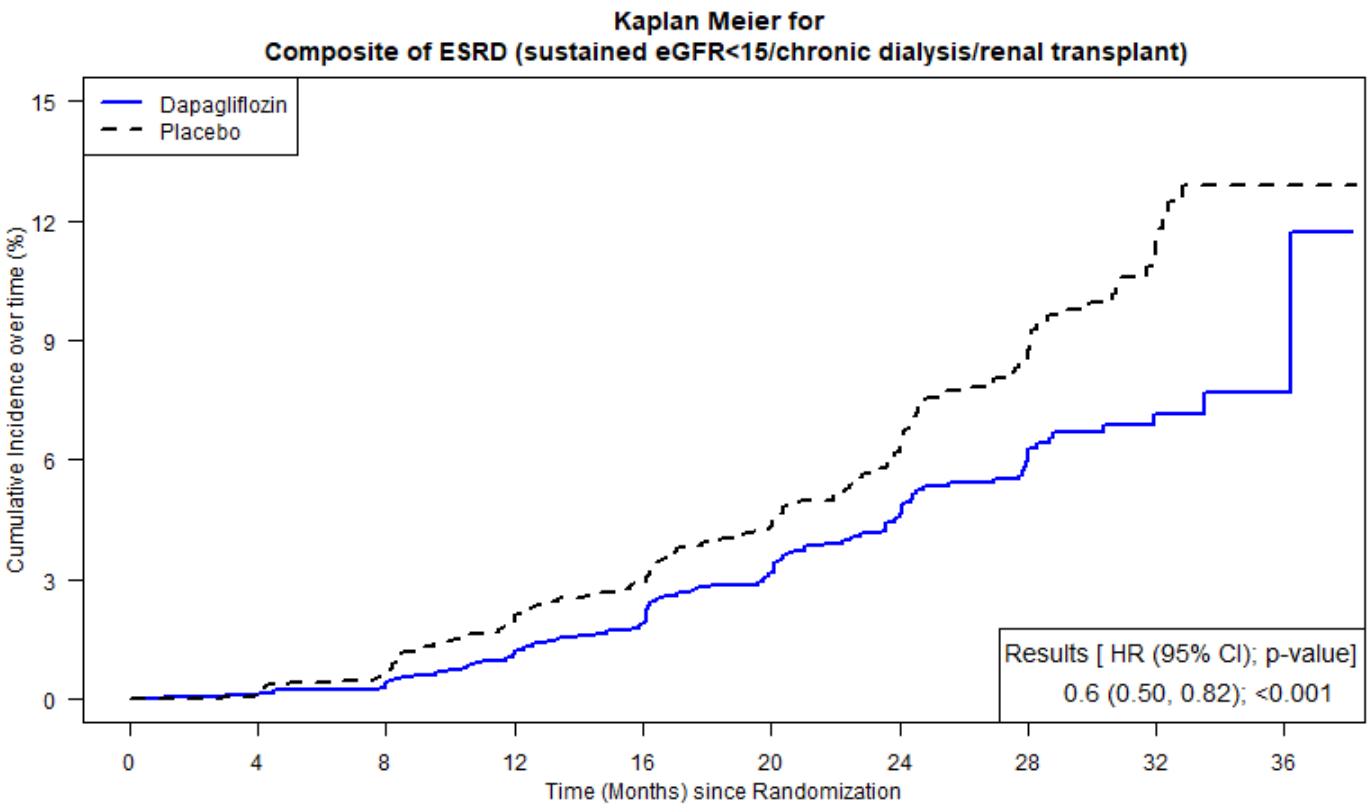
Figure 26 Kaplan-Meier Plot of Time-to-first Sustained ≥ 50% eGFR Decline (FAS)



Number of Events										
Dapagliflozin	0	4	14	25	39	66	84	98	110	112
Placebo	0	8	19	45	70	105	151	182	199	201
Number at Risk										
Dapagliflozin	2152	2002	1954	1899	1840	1706	1294	835	310	31
Placebo	2152	1995	1937	1862	1794	1670	1240	779	273	24
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.2	0.7	1.3	2.0	3.5	4.6	5.7	7.8	8.4
$\hat{F}_{Placebo}$	0.0	0.4	0.9	2.3	3.6	5.5	8.4	11.1	14.3	14.9

Abbreviations: eGFR=estimated glomerular filtration rate; HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

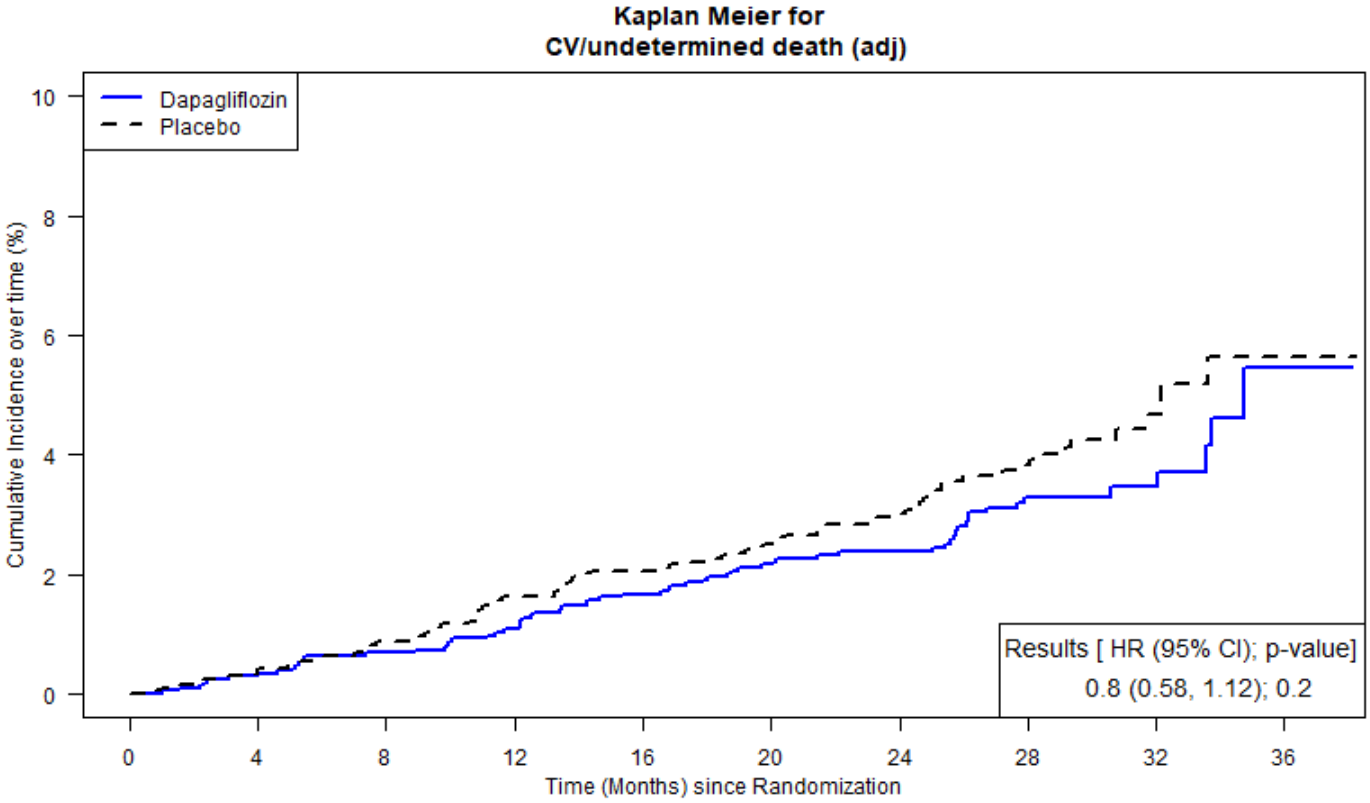
Figure 27 Kaplan-Meier Plot of Time-to-first ESKD (FAS)



Number of Events										
Dapagliflozin	0	3	8	23	37	60	83	99	107	108
Placebo	0	4	13	40	57	83	112	140	157	161
Number at Risk										
Dapagliflozin	2152	2004	1963	1908	1856	1724	1308	843	318	32
Placebo	2152	1997	1942	1874	1817	1700	1280	808	286	27
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.1	0.4	1.2	1.9	3.1	4.6	6.0	7.2	7.7
$\hat{F}_{Placebo}$	0.0	0.2	0.7	2.0	2.9	4.4	6.2	8.6	11.5	12.9

Abbreviations: eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

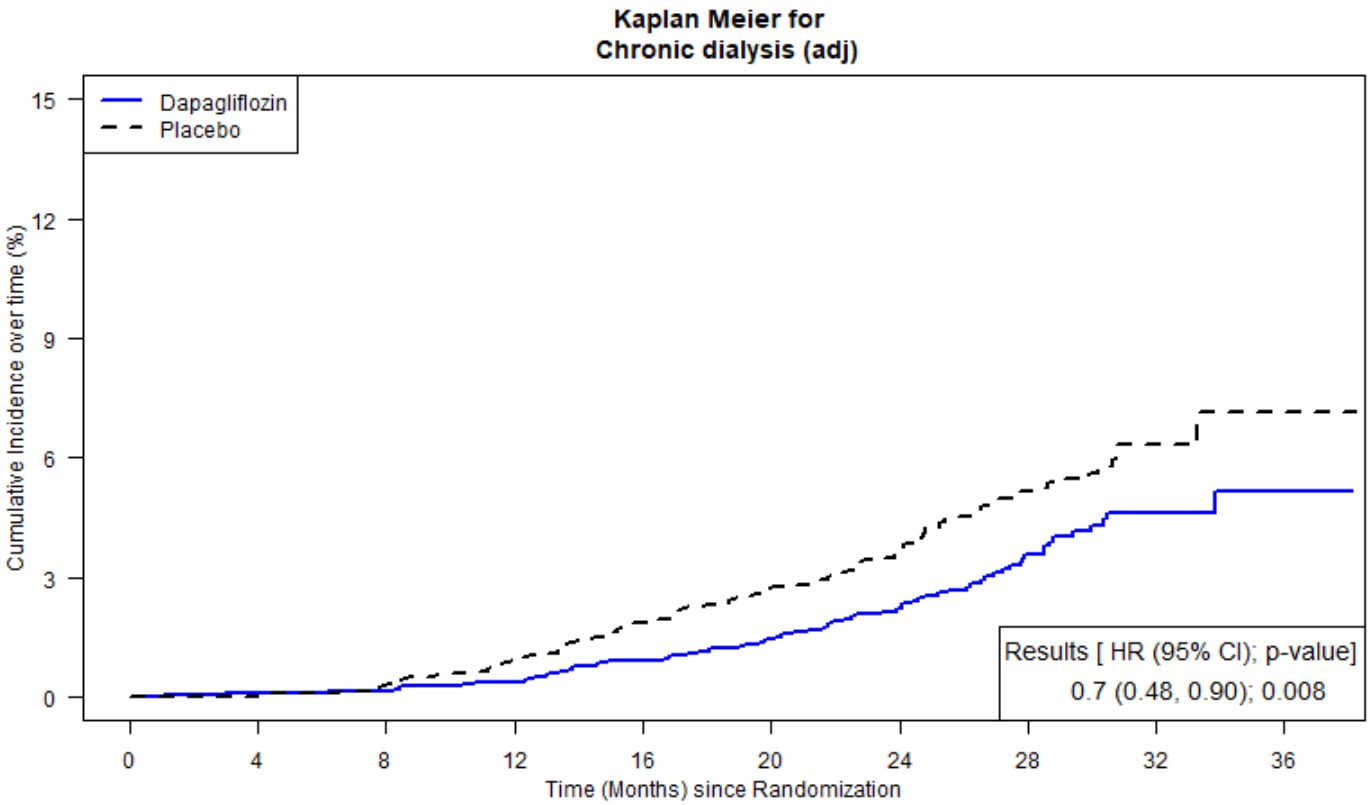
Figure 28 Kaplan-Meier plot of CV death (FAS)



Number of Events										
Dapagliflozin	0	7	14	22	34	44	48	60	61	65
Placebo	0	9	18	33	42	51	59	71	77	80
Number at Risk										
Dapagliflozin	2152	2037	2025	2013	1994	1920	1525	1024	398	43
Placebo	2152	2034	2017	1992	1971	1901	1502	1009	378	44
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.3	0.7	1.1	1.7	2.2	2.4	3.3	3.5	5.5
$\hat{F}_{Placebo}$	0.0	0.4	0.9	1.6	2.1	2.5	2.9	3.8	4.7	5.6

Abbreviations: CV=cardiovascular; adj=adjudicated; HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

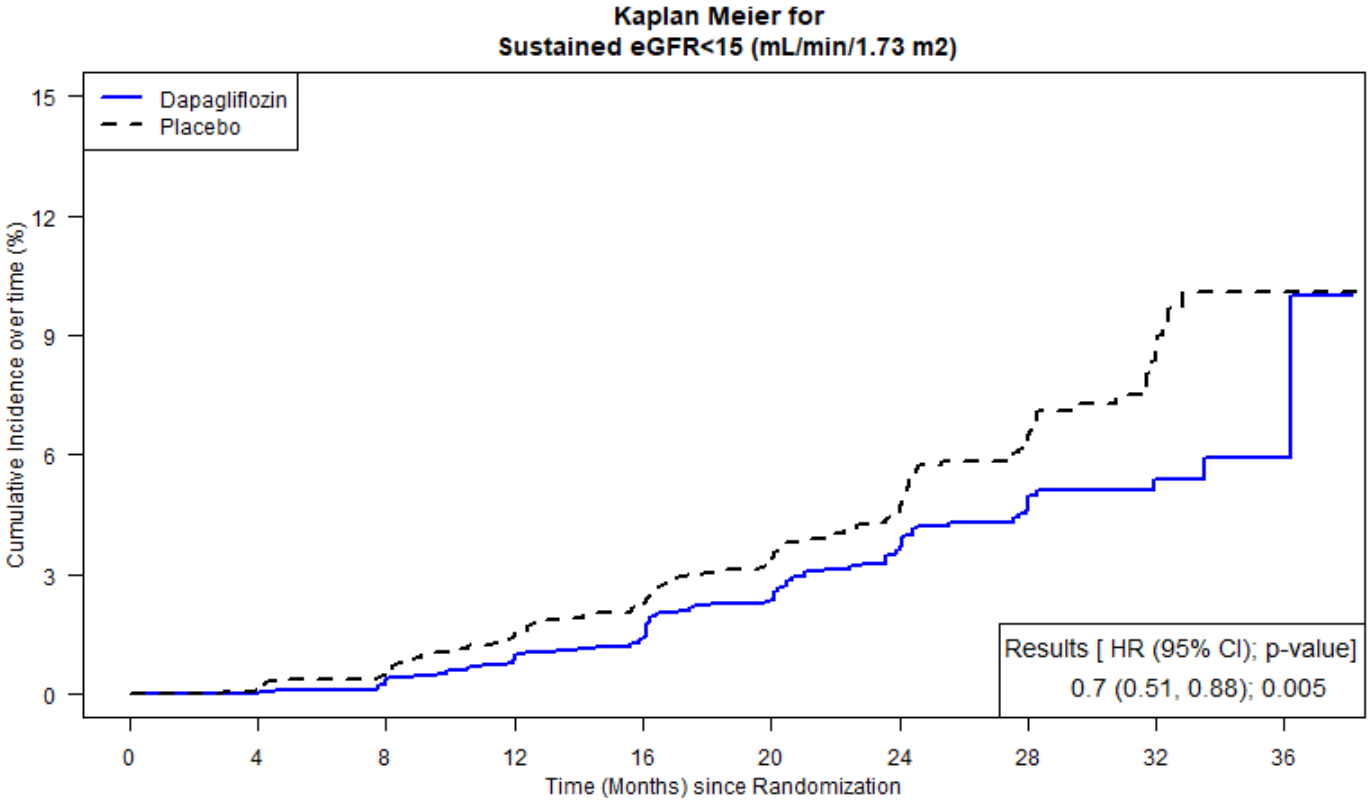
Figure 29 Kaplan-Meier plot of chronic dialysis (FAS)



Number of Events										
Dapagliflozin	0	2	3	7	18	29	42	59	67	68
Placebo	0	1	6	19	37	54	69	89	97	99
Number at Risk										
Dapagliflozin	2152	2035	2021	2004	1977	1887	1482	985	373	39
Placebo	2152	2031	2006	1971	1936	1850	1445	955	356	40
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.1	0.1	0.3	0.9	1.5	2.2	3.6	4.6	5.2
$\hat{F}_{Placebo}$	0.0	0.0	0.3	0.9	1.9	2.7	3.6	5.1	6.3	7.2

Abbreviations: HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

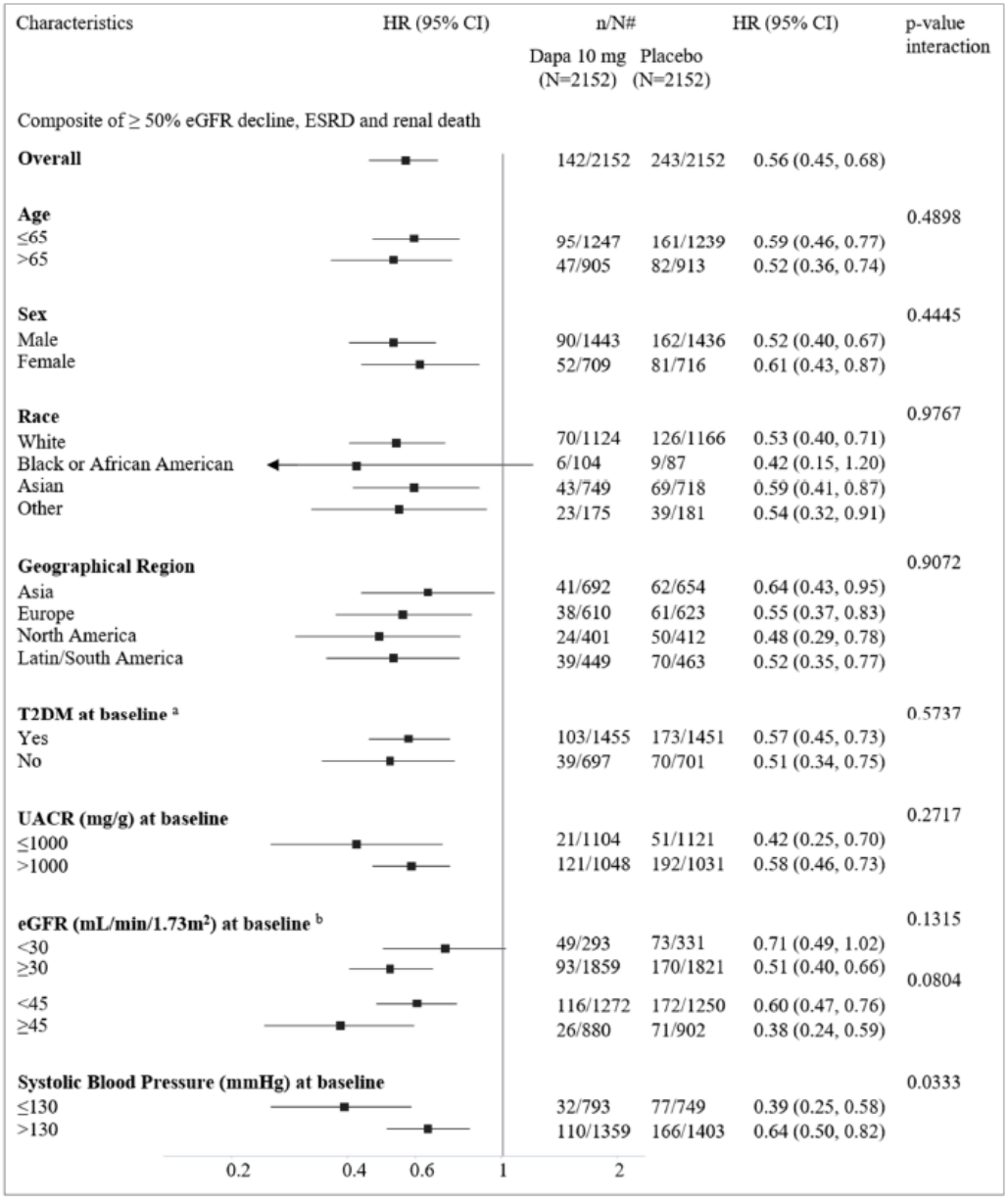
Figure 30 Kaplan-Meier plot of sustained eGFR<15 ml/min/1.73m^2 (FAS)



Number of Events										
Dapagliflozin	0	1	7	18	27	45	65	77	82	83
Placebo	0	3	9	29	43	63	83	103	116	120
Number at Risk										
Dapagliflozin	2152	2005	1961	1907	1853	1726	1309	846	318	32
Placebo	2152	1998	1942	1875	1816	1700	1284	812	288	27
Cumulative Incidence (%)										
$\hat{F}_{Dapagliflozin}$	0.0	0.0	0.4	0.9	1.4	2.4	3.6	4.6	5.4	5.9
$\hat{F}_{Placebo}$	0.0	0.1	0.5	1.5	2.2	3.3	4.6	6.3	8.7	10.1

Abbreviations: eGFR=estimated glomerular filtration rate; HR=hazard ratio; CI=confidence interval; FAS=full analysis set
Source: Statistical reviewer

Figure 31 Forest plot of the composite of ≥50% eGFR decline, ESKD and renal death by subgroups (FAS)



[a] Defined as history of T2DM or HbA1c ≥ 6.5% at both visit 1 and visit 2. n/N# = Number of subjects with event / number of subjects in the subgroup.

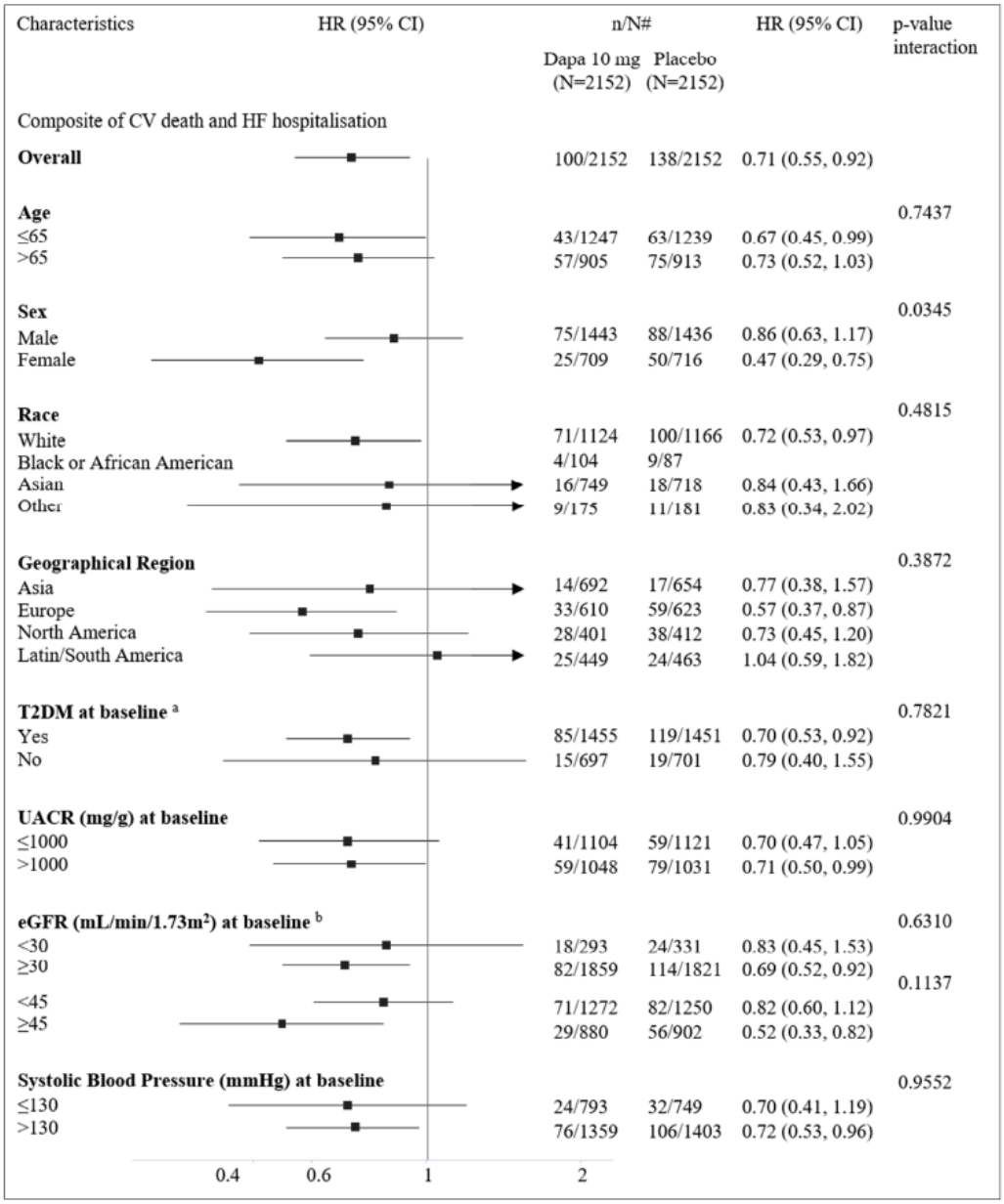
[b] This analysis does not adjust for baseline eGFR.

Event rates are presented as the number of subjects with event per 100 patient-years of follow-up.
Hazard ratio, CI and p-value are calculated from Cox proportional hazards model stratified by randomisation stratification of T2DM status and UACR, adjusting for baseline eGFR, with factors for treatment group, subgroup, and the interaction between treatment group and the subgroup variable.

Subgroup analyses for T2DM only use UACR as stratification variable in the model and vice versa. Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

CI, confidence interval; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FAS, full analysis set; HbA1c: glycated haemoglobin; N, number of subjects; n, number of subjects included in analysis; T2DM, type 2 diabetes mellitus; UACR, urine albumin creatinine ratio.

Figure 32 Forest plot of the composite of CV death and hospitalization for heart failure by subgroups (FAS)



[a] Defined as history of T2DM or HbA1c ≥ 6.5% at both visit 1 and visit 2. n/N# = Number of subjects with event / number of subjects in the subgroup.

[b] This analysis does not adjust for baseline eGFR.

Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

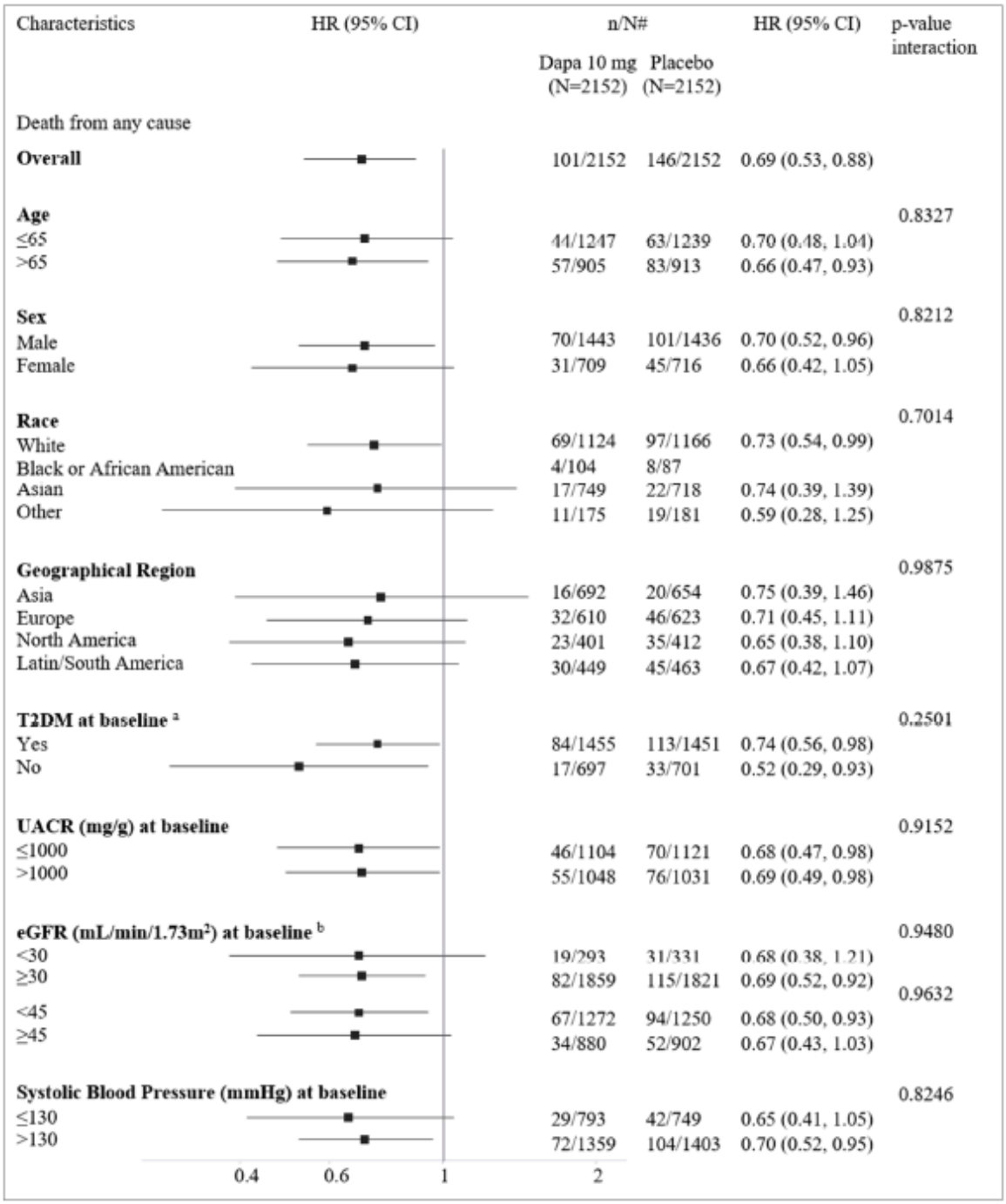
Hazard ratio, CI and p-value are calculated from Cox proportional hazards model stratified by randomisation stratification of T2DM status and UACR, adjusting for baseline eGFR, with factors for treatment group, subgroup, and the interaction between treatment group and the subgroup variable.

Subgroup analyses for T2DM only use UACR as stratification variable in the model and vice versa. Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HbA1c, glycated haemoglobin; N, number of subjects; n, number of subjects included in analysis; T2DM, type 2 diabetes mellitus; UACR, urine albumin creatinine ratio.

Source: CSR, Figure 9

Figure 33 Forest plot of the time to death from any cause by subgroups (FAS)

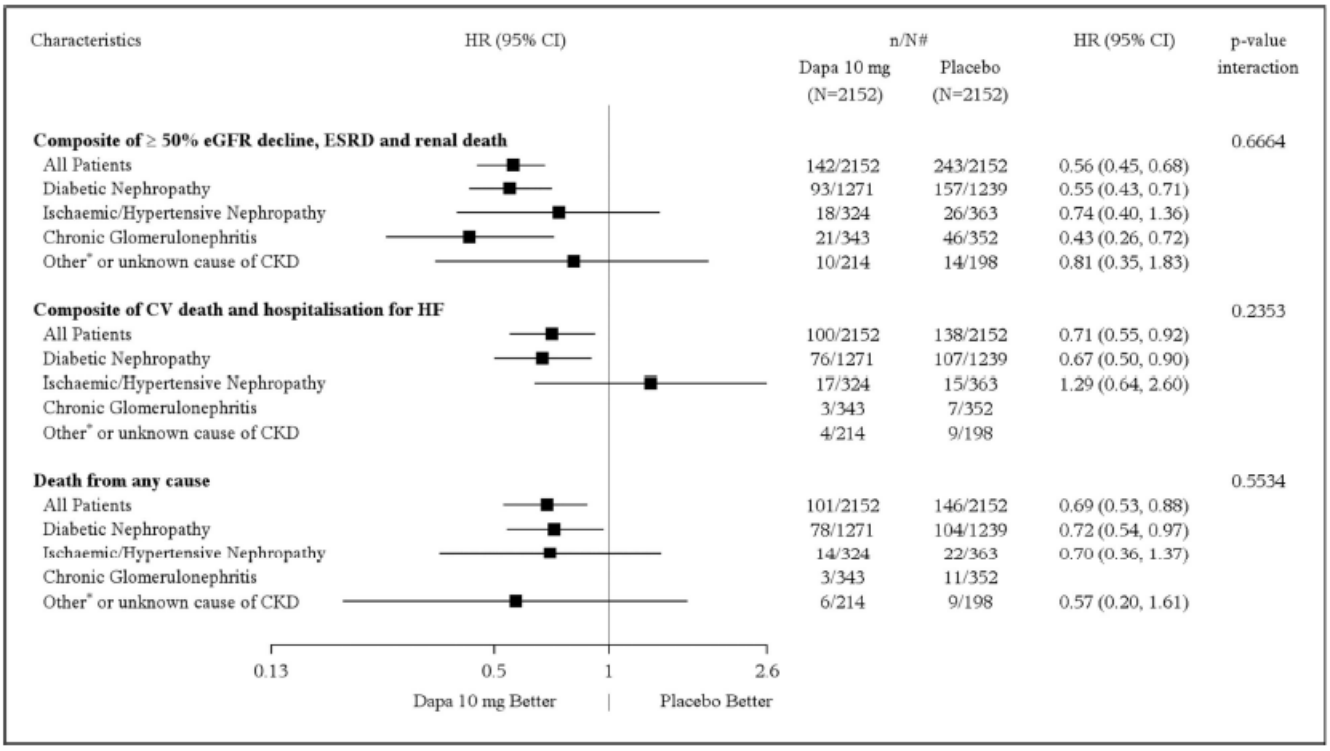


[a] Defined as history of T2DM or HbA1c ≥ 6.5% at both visit 1 and visit 2. n/N# = Number of subjects with event / number of subjects in the subgroup.

[b] This analysis does not adjust for baseline eGFR. Event rates are presented as the number of subjects with event per 100 patient-years of follow-up.

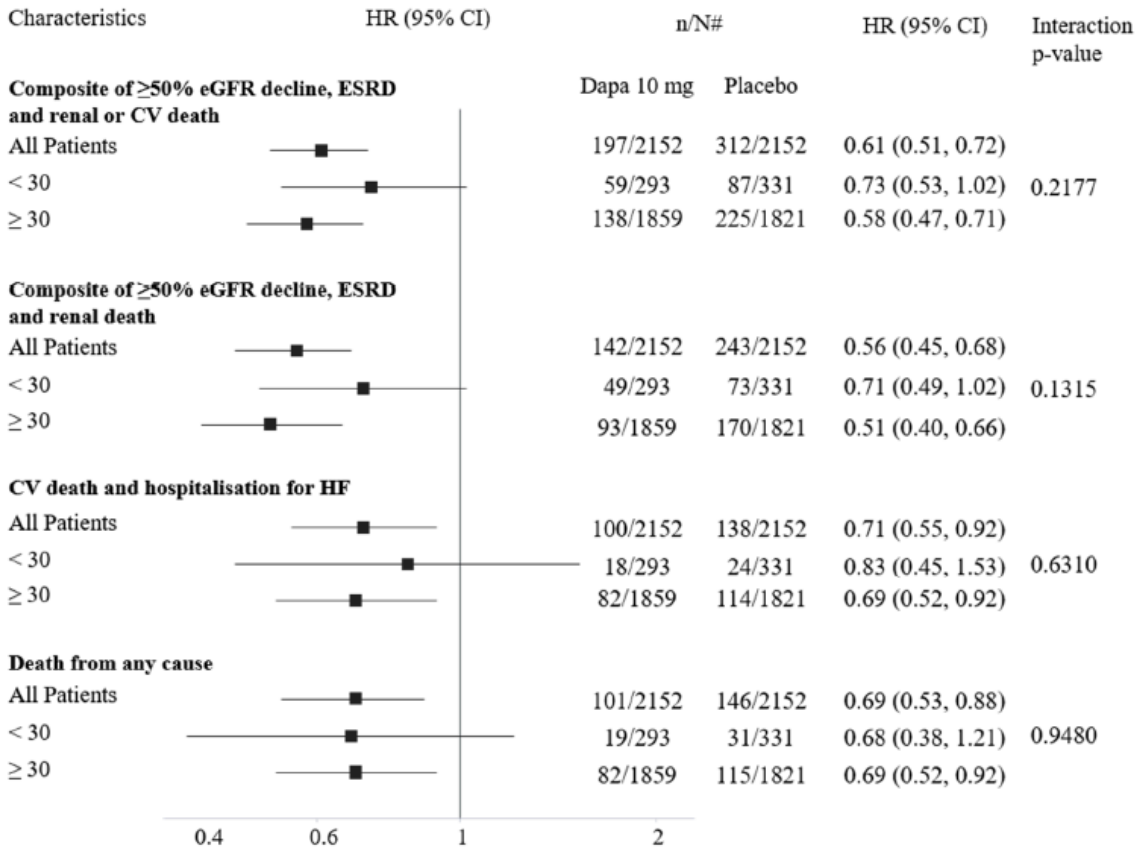
Source: CSR, Figure 11

Figure 34 Forest plot of the secondary endpoints by CKD etiologies (FAS)



Source: March 3, 2021 Information Request Figure 1.

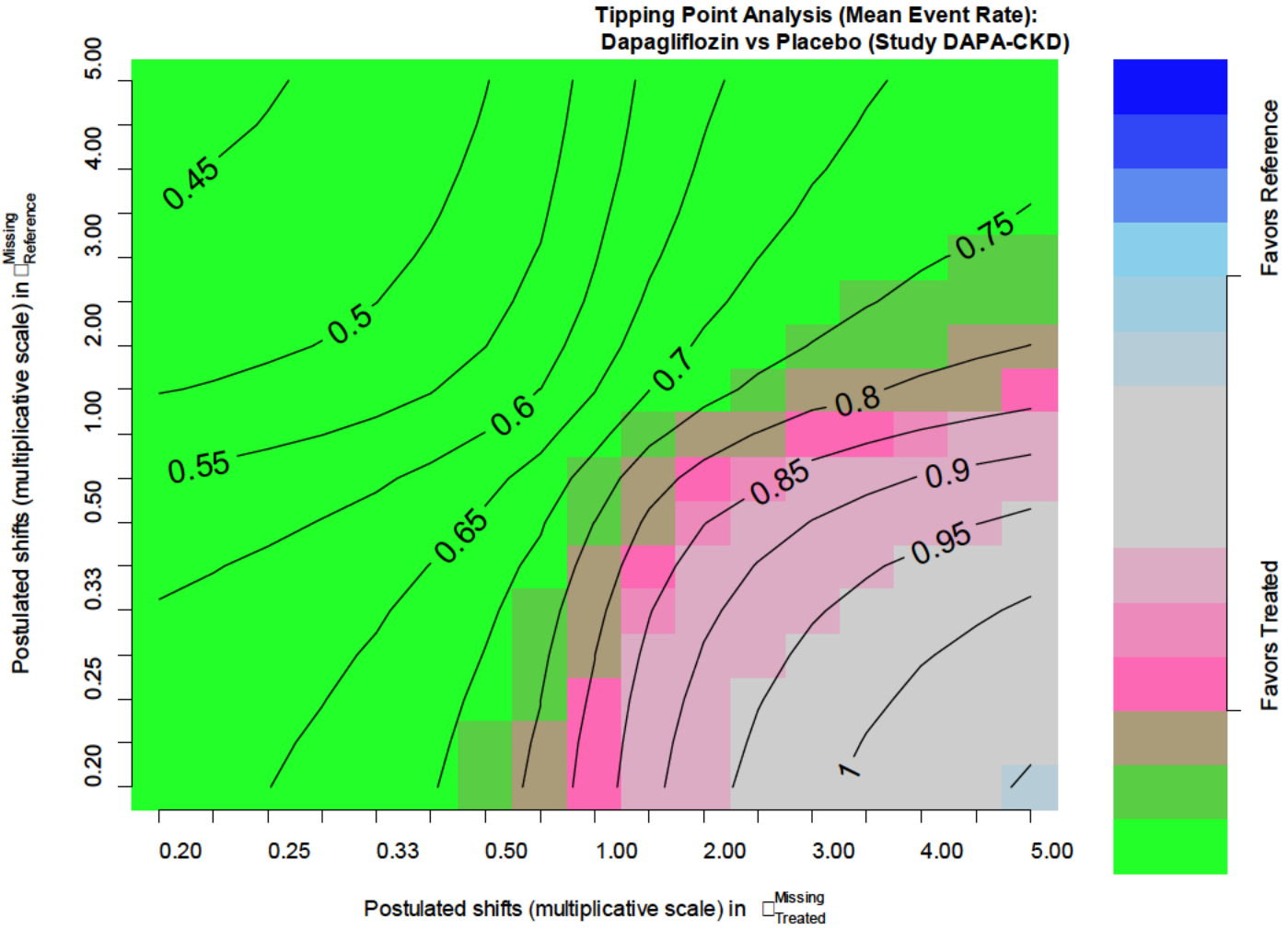
Figure 35 Forest plot of the primary and secondary endpoints by baseline eGFR<30 and >30 mL/min/1.73m^2 (FAS)



Hazard ratio, CI and p-value for subgroup analysis by baseline renal function are calculated from Cox proportional hazards model stratified by randomisation stratification of T2DM status and UACR, adjusting for baseline eGFR, with factors for treatment group, subgroup, and the interaction between treatment group and the subgroup variable. Hazard ratio estimates are not presented for categories with less than 15 events in total (both arms combined).
CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FAS, full analysis set; HF, heart failure; HR, hazard ratio; n, number of patients with events; N#, number of subjects in subgroup; T2DM, type 2 diabetes mellitus; UACR, urine albumin creatinine ratio.
Derived from: DAPA-CKD CSR Tables 14.2.1, 14.2.2.3, 14.2.3.2, 14.2.4.2, and 14.2.5.2 in CTD Module 5.3.5.1.

Source: Clinical Overview, Figure 9

Figure 36 Tipping Point Analysis Using the Applicant's Multiple Imputation According to On-treatment and Off-treatment Hazard Rates



The hazard rates for the on- and off-treatment were shifted together on the multiplicative scale ranging from 0.2 to 5. A multiplicative scale of 1 for both placebo and dapagliflozin arm, corresponds to the Applicant's additional multiple imputation of 0.68 (95% CI 0.58, 0.81). A scale larger than 1 indicates a higher number of events compared to the reference starting rates; A scale smaller than 1 indicates a lower number of events. The contour lines in the figure represent the estimated hazard ratios (combined using Rubin's rule). The colors ranging from pink to grey represent the non-statistical significance of 2-sided p> 0.05. In order for the Applicant's results to tip, the estimated on- and off-treatment rates for patients missing follow-up in the placebo arm would have to at least halved while holding the hazard rates for those patients with missing follow-up on dapagliflozin arm rates fixed. This scenario is likely implausible due to the lack of available alternative therapies.

Source: Statistical reviewer

12.8.1. Additional Efficacy Tables

Table 53 Results for the Percent Change from Baseline in UACR Comparing Dapagliflozin with Placebo

Visit Weeks	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)	Dapa vs Placebo Difference (95% CI)
Visit 3 (14 days)	-33.1 (-34.8, -31.5)	-15.5 (-17.6, -13.4)	-20.9 (-23.6, -18.1)
Visit 4 (2 Months)	-39.8 (-41.7, -37.8)	-18.7 (-21.3, -16.1)	-25.9 (-29.2, -22.4)
Visit 5 (4 Months)	-40.9 (-43.0, -38.6)	-19.1 (-22.0, -16.0)	-26.9 (-30.6, -23.0)
Visit 6 (8 Months)	-43.2 (-45.6, -40.6)	-15.7 (-19.4, -11.8)	-32.6 (-36.7, -28.2)
Visit 7 (12 Months)	-46.4 (-48.8, -43.8)	-19.4 (-23.1, -15.5)	-33.5 (-37.8, -29.0)
Visit 8 (16 Months)	-46.5 (-49.2, -43.7)	-22.7 (-26.6, -18.6)	-30.9 (-35.7, -25.7)
Visit 9 (20 Months)	-44.1 (-47.2, -40.8)	-20.9 (-25.3, -16.3)	-29.3 (-34.8, -23.4)
Visit 10 (24 Months)	-45.2 (-48.4, -41.9)	-21.0 (-25.6, -16.0)	-30.7 (-36.4, -24.6)
Visit 11 (28 Months)	-45.7 (-49.2, -41.9)	-19.8 (-25.1, -14.2)	-32.2 (-38.4, -25.4)
Visit 12 (32 Months)	-43.3 (-47.5, -38.7)	-16.1 (-22.5, -9.2)	-32.4 (-39.5, -24.4)
Visit 13 (36 Months)	-41.1 (-47.1, -34.4)	-20.1 (-28.4, -10.8)	-26.3 (-36.8, -14.0)

The MMRM regression model was fit to the change from baseline in the logarithm of the UACR adjusting for treatment group, baseline logarithm UACR, visit week, interaction of visit by treatment with unstructured variance-covariance matrix.
Negative values of the percent change represent a decline in UACR compared to baseline.
Abbreviations: LS=least squares; T2DM=Type 2 diabetes mellitus; UACR=urine albumin-to-creatinine ratio; CI=confidence interval
Source: Statistical reviewer

Table 54 Results for the Percent Change from Baseline in UACR by Baseline T2DM Status

Baseline T2DM Status	Visit Weeks	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)	Dapa vs Placebo Difference (95% CI)
Without T2DM	14 days	-25.7 (-28.6, -22.8)	-15.6 (-18.9, -12.3)	-11.9 (-16.7, -7.0)
	2 Months	-31.2 (-34.6, -27.5)	-19.6 (-23.6, -15.4)	-14.4 (-20.4, -7.9)
	4 Months	-35.1 (-39.0, -30.9)	-19.1 (-24.0, -14.0)	-19.7 (-26.4, -12.4)
	8 Months	-33.2 (-37.9, -28.2)	-17.1 (-22.8, -10.9)	-19.5 (-27.3, -10.8)
	12 Months	-37.2 (-42.0, -32.1)	-21.6 (-27.5, -15.2)	-19.9 (-28.3, -10.5)
	16 Months	-36.7 (-41.7, -31.3)	-23.5 (-29.6, -17.0)	-17.3 (-26.3, -7.1)
	20 Months	-31.0 (-37.0, -24.5)	-23.3 (-30.0, -16.1)	-10.0 (-20.8, 2.2)
	24 Months	-36.1 (-42.1, -29.5)	-24.0 (-31.1, -16.2)	-15.9 (-26.8, -3.4)
	28 Months	-35.2 (-42.5, -26.9)	-25.2 (-33.7, -15.7)	-13.3 (-26.8, 2.8)
	32 Months	-25.7 (-34.5, -15.7)	-17.0 (-27.0, -5.6)	-10.5 (-25.2, 7.2)
	36 Months	-41.9 (-51.9, -29.8)	-26.2 (-39.1, -10.6)	-21.3 (-39.9, 3.1)
With T2DM	14 days	-36.5 (-38.4, -34.5)	-15.5 (-18.1, -12.8)	-24.8 (-28.1, -21.4)
	2 Months	-43.5 (-45.8, -41.1)	-18.3 (-21.6, -14.9)	-30.8 (-34.7, -26.7)
	4 Months	-43.5 (-46.0, -40.8)	-19.1 (-22.7, -15.2)	-30.1 (-34.5, -25.5)
	8 Months	-47.3 (-50.2, -44.3)	-15.0 (-19.6, -10.1)	-38.0 (-42.8, -32.9)
	12 Months	-50.2 (-53.0, -47.3)	-18.2 (-22.9, -13.3)	-39.1 (-44.0, -34.0)
	16 Months	-50.6 (-53.7, -47.4)	-22.3 (-27.2, -17.1)	-36.4 (-42.0, -30.4)
	20 Months	-49.4 (-52.9, -45.6)	-19.7 (-25.3, -13.7)	-36.9 (-43.0, -30.2)
	24 Months	-49.1 (-52.8, -45.1)	-19.4 (-25.3, -13.0)	-36.9 (-43.3, -29.7)
	28 Months	-50.0 (-53.9, -45.8)	-17.4 (-23.9, -10.3)	-39.5 (-46.1, -32.1)
	32 Months	-49.7 (-54.4, -44.6)	-15.7 (-23.7, -6.8)	-40.4 (-48.1, -31.5)
	36 Months	-41.3 (-48.4, -33.2)	-15.2 (-25.6, -3.4)	-30.8 (-42.4, -16.8)

Within each T2DM subcategory, the MMRM regression model was fit to the change from baseline in the logarithm of the UACR adjusting for treatment group, baseline logarithm UACR, visit week, interaction of visit by treatment with unstructured variance-covariance matrix.
Negative values of the percent change represent a decline in UACR compared to baseline.
Abbreviations: LS=least squares; T2DM=Type 2 diabetes mellitus; UACR=urine albumin-to-creatinine ratio; CI=confidence interval
Source: Statistical reviewer

Table 55 Summary Statistics for KDQOL Score at Visit Weeks

Components of KDQOL	Visit	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)	Dapagliflozin 10 mg		Placebo	
				Change from Baseline	N	Change from Baseline	N
PCS	Baseline	43.14 (9.5)	42.64 (9.5)	-	2013	-	2019
	12 Months	43.35 (9.5)	42.76 (9.6)	-0.08 (8.5)	1821	-0.10 (8.5)	1819
	24 Months	43.56 (9.5)	42.40 (9.5)	0.05 (8.9)	1509	-0.36 (9.2)	1461
	36 Months	43.37 (9.4)	42.85 (9.9)	0.15 (8.9)	998	0.20 (9.8)	956
MCS	Baseline	49.77 (9.6)	49.93 (9.6)	-	2013	-	2019
	12 Months	49.73 (9.8)	49.34 (9.9)	-0.33 (9.9)	1821	-0.74 (10.2)	1819
	24 Months	49.92 (9.6)	49.30 (9.8)	-0.22 (10.1)	1509	-0.77 (10.6)	1461
	36 Months	49.19 (9.8)	49.15 (10.1)	-0.06 (10.9)	998	-0.75 (11.1)	956
Symptoms of kidney disease score	Baseline	82.01 (14.4)	81.91 (14.2)	-	2013	-	2019
	12 Months	82.59 (14.2)	81.89 (14.3)	0.33 (12.6)	1821	-0.18 (12.6)	1819
	24 Months	82.31 (14.6)	81.10 (14.9)	0.05 (13.1)	1509	-0.71 (13.6)	1461
	36 Months	82.55 (14.1)	82.03 (14.6)	1.45 (13.8)	998	0.20 (14.7)	956
Burden of kidney disease score	Baseline	68.21 (26.1)	67.75 (26.2)	-	2013	-	2019
	12 Months	70.03 (25.4)	69.63 (25.9)	1.49 (24.1)	1821	1.61 (24.6)	1819
	24 Months	71.54 (25.2)	70.02 (25.2)	1.74 (25.4)	1509	0.87 (25.1)	1461
	36 Months	70.82 (25.4)	69.78 (26.3)	2.30 (25.6)	998	0.90 (27.1)	956
Effects of kidney disease score	Baseline	84.29 (16.1)	84.09 (15.6)	-	2013	-	2019
	12 Months	86.03 (14.9)	85.09 (15.5)	1.37 (14.7)	1821	0.77 (15.2)	1819
	24 Months	85.79 (15.6)	84.35 (16.1)	0.70 (15.4)	1509	-0.12 (16.0)	1461
	36 Months	84.73 (16.1)	84.79 (16.4)	0.14 (16.0)	998	0.62 (17.4)	956

Abbreviations: PCS=Physical component score; MCS=mental component score; KDQOL=kidney disease quality of life
Source: Statistical reviewer

Table 56 Summary Statistics for the EQ-5D-QOL at Visit Weeks

Visit	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)	Dapagliflozin 10 mg		Placebo	
			Change from Baseline	N	Change from Baseline	N
Baseline	0.78 (0.2)	0.78 (0.2)	-	1983	-	1995
4 Month	0.80 (0.2)	0.80 (0.2)	0.02 (0.2)	1865	0.01 (0.2)	1883
8 Months	0.80 (0.2)	0.80 (0.2)	0.02 (0.2)	1724	0.01 (0.2)	1716
12 Months	0.78 (0.2)	0.77 (0.2)	-0.00 (0.2)	1667	-0.01 (0.2)	1652
24 Months	0.79 (0.2)	0.78 (0.2)	0.00 (0.2)	1481	-0.01 (0.2)	1436
36 Months	0.79 (0.2)	0.77 (0.2)	0.01 (0.2)	980	-0.00 (0.2)	939

Abbreviations: EQ-5D-5L=EuroQol five-dimensional five-level questionnaire.
Source: Statistical reviewer

Table 57 Adjudicated deaths which are part of the efficacy analysis by adjudication category (CV death, non-CV death and undetermined cause of death), System Organ Class and by Preferred Term

System Organ Class	Preferred Term	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
All deaths		**101 (4.7)**	**146 (6.8)**	**247 (5.7)**
CV deaths				
Cardiac disorders	Acute left ventricular failure	0 (0)	1 (0)	1 (0)
	Acute myocardial infarction	7 (0.3)	9 (0.4)	16 (0.4)
	Angina unstable	1 (0)	0 (0)	1 (0)
	Atrial fibrillation	1 (0)	0 (0)	1 (0)
	Cardiac arrest	0 (0)	6 (0.3)	6 (0.1)
	Cardiac failure	3 (0.1)	6 (0.3)	9 (0.2)
	Cardiac failure acute	2 (0.1)	0 (0)	2 (0)
	Cardiac failure chronic	0 (0)	1 (0)	1 (0)
	Cardiac failure congestive	0 (0)	2 (0.1)	2 (0)
	Cardiogenic shock	1 (0)	0 (0)	1 (0)
	Cardio-respiratory arrest	3 (0.1)	1 (0)	4 (0.1)
	Coronary artery disease	1 (0)	0 (0)	1 (0)
	Ischemic cardiomyopathy	0 (0)	1 (0)	1 (0)
	Myocardial infarction	2 (0.1)	2 (0.1)	4 (0.1)
	Myocardial ischemia	2 (0.1)	0 (0)	2 (0)
	Ventricular tachycardia	1 (0)	0 (0)	1 (0)
	All	24 (1.1)	29 (1.3)	53 (1.2)
Gastrointestinal disorders	Thrombosis mesenteric vessel	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)
General disorders and administration site conditions	Cardiac death	0 (0)	1 (0)	1 (0)
	Death	4 (0.2)	5 (0.2)	9 (0.2)
	Multiple organ dysfunction syndrome	1 (0)	0 (0)	1 (0)
	Sudden cardiac death	1 (0)	0 (0)	1 (0)
	Sudden death	3 (0.1)	1 (0)	4 (0.1)
	All	9 (0.4)	7 (0.3)	16 (0.4)
Metabolism and nutrition disorders	Diabetes mellitus	0 (0)	1 (0)	1 (0)
	Type 2 diabetes mellitus	0 (0)	1 (0)	1 (0)
	All	0 (0)	2 (0.1)	2 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-small cell lung cancer	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)

System Organ Class	Preferred Term	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
Nervous system disorders	Cerebellar stroke	0 (0)	1 (0)	1 (0)
	Cerebrovascular accident	1 (0)	1 (0)	2 (0)
	Hemorrhagic stroke	1 (0)	1 (0)	2 (0)
	Ischemic stroke	2 (0.1)	2 (0.1)	4 (0.1)
	Subarachnoid hemorrhage	1 (0)	0 (0)	1 (0)
	All	5 (0.2)	5 (0.2)	10 (0.2)
Renal and urinary disorders	End stage kidney disease	1 (0)	1 (0)	2 (0)
	All	1 (0)	1 (0)	2 (0)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	0 (0)	1 (0)	1 (0)
	Pulmonary embolism	1 (0)	0 (0)	1 (0)
	Pulmonary edema	0 (0)	1 (0)	1 (0)
	All	1 (0)	2 (0.1)	3 (0.1)
Vascular disorders	Aortic aneurysm rupture	1 (0)	0 (0)	1 (0)
	Hypertension	0 (0)	1 (0)	1 (0)
	Hypovolemic shock	0 (0)	1 (0)	1 (0)
	All	1 (0)	2 (0.1)	3 (0.1)
All CV-deaths	All	41 (1.9)	50 (2.3)	91 (2.1)
Undetermined deaths				
Cardiac disorders	Cardiac arrest	1 (0)	0 (0)	1 (0)
	Cardiac failure	1 (0)	1 (0)	2 (0)
	Cardiac failure congestive	0 (0)	2 (0.1)	2 (0)
	Cardiogenic shock	0 (0)	1 (0)	1 (0)
	Cardiomyopathy	0 (0)	1 (0)	1 (0)
	Coronary artery disease	0 (0)	1 (0)	1 (0)
	Myocardial infarction	3 (0.1)	1 (0)	4 (0.1)
	All	5 (0.2)	7 (0.3)	12 (0.3)
Gastrointestinal disorders	Mesenteric vascular insufficiency	1 (0)	0 (0)	1 (0)
	All	1 (0)	0 (0)	1 (0)
General disorders and administration site conditions	Death	11 (0.5)	16 (0.7)	27 (0.6)
	Sudden cardiac death	0 (0)	1 (0)	1 (0)
	Sudden death	1 (0)	0 (0)	1 (0)
	All	12 (0.6)	17 (0.8)	29 (0.7)
Hepatobiliary disorders	Hepatic cirrhosis	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)
Infections and infestations	Pneumonia	0 (0)	1 (0)	1 (0)

System Organ Class	Preferred Term	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
	Pulmonary sepsis	1 (0)	0 (0)	1 (0)
	Sepsis	0 (0)	1 (0)	1 (0)
	All	1 (0)	2 (0.1)	3 (0.1)
Metabolism and nutrition disorders	Hyperglycemia	1 (0)	0 (0)	1 (0)
	All	1 (0)	0 (0)	1 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)
Nervous system disorders	Ischemic stroke	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)
Renal and urinary disorders	End stage kidney disease	1 (0)	0 (0)	1 (0)
	Renal failure	1 (0)	0 (0)	1 (0)
	All	2 (0.1)	0 (0)	2 (0)
Respiratory, thoracic and mediastinal disorders	Acute pulmonary edema	2 (0.1)	0 (0)	2 (0)
	Pulmonary embolism	0 (0)	1 (0)	1 (0)
	All	2 (0.1)	1 (0)	3 (0.1)
All undetermined deaths	All	24 (1.1)	30 (1.4)	54 (1.3)
Non-CV deaths				
Cardiac disorders	Acute myocardial infarction	0 (0)	1 (0)	1 (0)
	Cardiac arrest	2 (0.1)	1 (0)	3 (0.1)
	Cardio-respiratory arrest	1 (0)	0 (0)	1 (0)
	All	3 (0.1)	2 (0.1)	5 (0.1)
Gastrointestinal disorders	Gastrointestinal hemorrhage	0 (0)	1 (0)	1 (0)
	Hemoperitoneum	1 (0)	0 (0)	1 (0)
	Upper gastrointestinal hemorrhage	0 (0)	2 (0.1)	2 (0)
	All	1 (0)	3 (0.1)	4 (0.1)
General disorders and administration site conditions	Death	0 (0)	1 (0)	1 (0)
	Multiple organ dysfunction syndrome	1 (0)	0 (0)	1 (0)
	All	1 (0)	1 (0)	2 (0)

System Organ Class	Preferred Term	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
Hepatobiliary disorders	Cholecystitis acute	0 (0)	1 (0)	1 (0)
	Hepatic cirrhosis	0 (0)	1 (0)	1 (0)
	Hepatic failure	0 (0)	1 (0)	1 (0)
	All	0 (0)	3 (0.1)	3 (0.1)
Infections and infestations	Bacterial sepsis	0 (0)	1 (0)	1 (0)
	Device related sepsis	1 (0)	0 (0)	1 (0)
	Gastroenteritis	1 (0)	0 (0)	1 (0)
	Pneumonia	3 (0.1)	9 (0.4)	12 (0.3)
	Pneumonia bacterial	0 (0)	1 (0)	1 (0)
	Sepsis	1 (0)	6 (0.3)	7 (0.2)
	Septic shock	5 (0.2)	9 (0.4)	14 (0.3)
	Skin infection	1 (0)	0 (0)	1 (0)
	Staphylococcal sepsis	1 (0)	0 (0)	1 (0)
	All	13 (0.6)	26 (1.2)	39 (0.9)
Injury, poisoning and procedural complications	Head injury	1 (0)	0 (0)	1 (0)
	Injury	1 (0)	0 (0)	1 (0)
	All	2 (0.1)	0 (0)	2 (0)
Metabolism and nutrition disorders	Lactic acidosis	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukemia	0 (0)	1 (0)	1 (0)
	Adenocarcinoma	1 (0)	0 (0)	1 (0)
	Adenocarcinoma gastric	0 (0)	1 (0)	1 (0)
	Adenocarcinoma pancreas	0 (0)	1 (0)	1 (0)
	Colon cancer	1 (0)	0 (0)	1 (0)
	Gallbladder cancer metastatic	0 (0)	1 (0)	1 (0)
	Hepatic cancer	0 (0)	1 (0)	1 (0)
	Hepatic cancer metastatic	0 (0)	1 (0)	1 (0)
	Hepatocellular carcinoma	1 (0)	0 (0)	1 (0)
	Laryngeal cancer	1 (0)	1 (0)	2 (0)
	Lung neoplasm	1 (0)	0 (0)	1 (0)
	Lung neoplasm malignant	1 (0)	4 (0.2)	5 (0.1)
	Lymphoplasmacytoid lymphoma/immunocytoma	1 (0)	0 (0)	1 (0)
	Non-small cell lung cancer	0 (0)	1 (0)	1 (0)

System Organ Class	Preferred Term	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
	Pancreatic carcinoma	0 (0)	1 (0)	1 (0)
	Prostate cancer metastatic	2 (0.1)	0 (0)	2 (0)
	Rectosigmoid cancer	0 (0)	1 (0)	1 (0)
	Small cell lung cancer	0 (0)	1 (0)	1 (0)
	All	9 (0.4)	15 (0.7)	24 (0.6)
Nervous system disorders	Brain injury	0 (0)	1 (0)	1 (0)
	Brain stem hemorrhage	0 (0)	1 (0)	1 (0)
	All	0 (0)	2 (0.1)	2 (0)
Psychiatric disorders	Completed suicide	0 (0)	1 (0)	1 (0)
	All	0 (0)	1 (0)	1 (0)
Renal and urinary disorders	Acute kidney injury	1 (0)	1 (0)	2 (0)
	Chronic kidney disease	1 (0)	1 (0)	2 (0)
	Cystitis hemorrhagic	0 (0)	1 (0)	1 (0)
	End stage kidney disease	0 (0)	3 (0.1)	3 (0.1)
	Renal failure	0 (0)	2 (0.1)	2 (0)
	Renal impairment	1 (0)	1 (0)	2 (0)
	All	3 (0.1)	9 (0.4)	12 (0.3)
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	1 (0)	0 (0)	1 (0)
	Chronic obstructive pulmonary disease	2 (0.1)	0 (0)	2 (0)
	Pneumonia aspiration	0 (0)	1 (0)	1 (0)
	Pulmonary fibrosis	1 (0)	0 (0)	1 (0)
	Respiratory failure	0 (0)	2 (0.1)	2 (0)
	All	4 (0.2)	3 (0.1)	7 (0.2)
All Non-CV deaths	All	36 (1.7)	66 (3.1)	102 (2.4)

Source: Clinical reviewer derived table from ADAE.xpt and ADTTE.xpt

Table 58. Non-CV deaths by Adjudication Subcategories of Infection (Includes Sepsis) and Malignancy and by PT term

Adjudication subcategory	PT term	Dapa 10 mg N=2152 N (%)	Placebo N=2152 N (%)	Total N=4304 N (%)
INFECTION (INCLUDES SEPSIS)	Acute kidney injury	1 (0.0)	0	1 (0.0)
	Acute myeloid leukemia	0	1 (0.0)	1 (0.0)
	Bacterial sepsis	0	1 (0.0)	1 (0.0)
	Brain injury	0	1 (0.0)	1 (0.0)
	Cardio-respiratory arrest	1 (0.0)	0	1 (0.0)

	Cholecystitis acute	0	1 (0.0)	1 (0.0)
	Device related sepsis	1 (0.0)	0	1 (0.0)
	Gastroenteritis	1 (0.0)	0	1 (0.0)
	Multiple organ dysfunction syndrome	1 (0.0)	0	1 (0.0)
	Pneumonia	3 (0.1)	8 (0.4)	11 (0.3)
	Pneumonia bacterial	0	1 (0.0)	1 (0.0)
	Prostate cancer metastatic	1 (0.0)	0	1 (0.0)
	Renal impairment	1 (0.0)	0	1 (0.0)
	Respiratory failure	0	1 (0.0)	1 (0.0)
	Sepsis	1 (0.0)	5 (0.2)	6 (0.1)
	Septic shock	5 (0.2)	9 (0.4)	14 (0.3)
	Skin infection	1 (0.0)	0	1 (0.0)
	Staphylococcal sepsis	1 (0.0)	0	1 (0.0)
	All	18 (0.8)	28 (1.3)	46 (1.1)
MALIGNANCY	Acute myocardial infarction	0	1 (0.0)	1 (0.0)
	Adenocarcinoma	1 (0.0)	0	1 (0.0)
	Adenocarcinoma gastric	0	1 (0.0)	1 (0.0)
	Adenocarcinoma pancreas	0	1 (0.0)	1 (0.0)
	Colon cancer	1 (0.0)	0	1 (0.0)
	Death	0	1 (0.0)	1 (0.0)
	Gallbladder cancer metastatic	0	1 (0.0)	1 (0.0)
	Hepatic cancer	0	1 (0.0)	1 (0.0)
	Hepatic cancer metastatic	0	1 (0.0)	1 (0.0)
	Hepatocellular carcinoma	1 (0.0)	0	1 (0.0)
	Laryngeal cancer	1 (0.0)	1 (0.0)	2 (0.0)
	Lung neoplasm	1 (0.0)	0	1 (0.0)
	Lung neoplasm malignant	1 (0.0)	4 (0.2)	5 (0.1)
	Lymphoplasmacytoid lymphoma/immunocytoma	1 (0.0)	0	1 (0.0)
	Non-small cell lung cancer	0	1 (0.0)	1 (0.0)
	Pancreatic carcinoma	0	1 (0.0)	1 (0.0)
	Pneumonia	0	1 (0.0)	1 (0.0)
	Prostate cancer metastatic	1 (0.0)	0	1 (0.0)
	Rectosigmoid cancer	0	1 (0.0)	1 (0.0)
	Renal impairment	0	1 (0.0)	1 (0.0)
	Sepsis	0	1 (0.0)	1 (0.0)
	Small cell lung cancer	0	1 (0.0)	1 (0.0)
	All	8 (0.4)	19 (0.9)	27 (0.6)

Source: Clinical reviewer derived from ADAE.xpt, FA.xpt, and ADTTE.xpt

12.9. DECLARE: additional efficacy analyses

Table 59 DECLARE- Subgroup analyses of the renal secondary composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m2, ESKD, renal death and or CV death)

	Dapa 10 mg (N=8582)			Placebo (N=8578)			
Subgroup Categories	N#	Subjects with events n(%)	Event rate	N#	Subjects with events n(%)	Event rate	Hazard ratio (95% CI)
Age (years)							
<65	4631	167 (3.6)	9.0	4622	226 (4.9)	12.3	0.72 (0.59, 0.88)
≥65	3951	203 (5.1)	12.8	3956	254 (6.4)	16.2	0.80 (0.67, 0.96)
Age (years)							
<75	8044	336 (4.2)	10.4	8020	436 (5.4)	13.7	0.76 (0.66, 0.87)
≥75	538	34 (6.3)	16.2	558	44 (7.9)	20.3	0.82 (0.52, 1.29)
Sex							
Male	5411	251 (4.6)	11.6	5327	302 (5.7)	14.3	0.81 (0.68, 0.96)
Female	3171	119 (3.8)	9.4	3251	178 (5.5)	13.8	0.68 (0.54, 0.86)
Race							
White	6843	299 (4.4)	10.8	6810	394 (5.8)	14.5	0.75 (0.64, 0.87)
Black or African American	295	12 (4.1)	10.2	308	21 (6.8)	17.6	0.56 (0.27, 1.13)
Asian	1148	42 (3.7)	9.5	1155	43 (3.7)	9.6	0.99 (0.65, 1.52)
American Indian or Alaska native	52	1 (1.9)	5.0	52	4 (7.7)	20.7	NA
Native Hawaiian or other Pacific Islander	9	0	0	13	0	0	NA
Other	235	16 (6.8)	17.4	240	18 (7.5)	19.8	0.86 (0.43, 1.69)
Ethnicity							
Hispanic or latino	1298	50 (3.9)	9.9	1270	75 (5.9)	15.6	0.64 (0.45, 0.92)
Not hispanic or latino	7284	320 (4.4)	10.9	7308	405 (5.5)	13.9	0.79 (0.68, 0.91)
Waist/hip ratio							
High (>0.90 (m), >0.85 (f))	7878	349 (4.4)	11.1	7885	445 (5.6)	14.2	0.78 (0.68, 0.90)
Low (≤0.90 (m), ≤0.85 (f))	641	20 (3.1)	7.9	627	31 (4.9)	12.7	0.63 (0.36, 1.10)
BMI (kg/m^2)							
<30	3432	141 (4.1)	10.4	3532	186 (5.3)	13.4	0.78 (0.62, 0.96)
≥30	5145	229 (4.5)	11.0	5042	292 (5.8)	14.5	0.76 (0.64, 0.90)
Duration of T2D (years)							
≤5	1887	73 (3.9)	9.7	1949	90 (4.6)	11.6	0.83 (0.61, 1.12)
>5	6695	297 (4.4)	11.1	6627	390 (5.9)	14.9	0.75 (0.64, 0.87)
≤10	4262	160 (3.8)	9.4	4305	202 (4.7)	11.8	0.80 (0.65, 0.98)
>10	4320	210 (4.9)	12.2	4271	278 (6.5)	16.5	0.74 (0.61, 0.88)
≤20	7523	316 (4.2)	10.5	7429	385 (5.2)	13.0	0.81 (0.69, 0.93)
>20	1059	54 (5.1)	12.9	1147	95 (8.3)	21.3	0.60 (0.43, 0.84)
DBP (mmHg)							
<80	4549	183 (4.0)	10.0	4618	258 (5.6)	14.1	0.72 (0.59, 0.87)
≥80	4033	187 (4.6)	11.7	3960	222 (5.6)	14.1	0.82 (0.67, 0.99)
SBP (mmHg)							
<130	3088	129 (4.2)	10.4	3155	152 (4.8)	12.1	0.86 (0.68, 1.08)
≥130	5494	241 (4.4)	11.0	5423	328 (6.0)	15.3	0.72 (0.61, 0.85)

Subgroup Categories	Dapa 10 mg (N=8582) N#	Subjects with events n(%)	Event rate	Placebo (N=8578) N#	Subjects with events n(%)	Event rate	Hazard ratio (95% CI)
DBP/SBP (mmHg)							
<80 and <130	2411	99 (4.1)	10.2	2448	125 (5.1)	12.9	0.80 (0.62, 1.04)
≥80 and ≥130	3356	157 (4.7)	11.8	3253	195 (6.0)	15.1	0.77 (0.63, 0.95)
(<80 and ≥130) or (≥80 and <130)	2815	114 (4.0)	10.1	2877	160 (5.6)	14.0	0.72 (0.57, 0.92)
Pulse pressure (mmHg)							
<60	5135	205 (4.0)	9.9	5226	250 (4.8)	12.0	0.82 (0.68, 0.99)
≥60	3447	165 (4.8)	12.1	3352	230 (6.9)	17.4	0.70 (0.57, 0.85)
HbA1c (%)							
<7	773	25 (3.2)	7.5	774	36 (4.7)	10.8	0.69 (0.41, 1.15)
≥7 - <8	3317	119 (3.6)	8.9	3309	171 (5.2)	13.0	0.69 (0.55, 0.87)
≥8 - <9	2193	100 (4.6)	11.5	2327	117 (5.0)	12.8	0.91 (0.70, 1.19)
≥9	2297	126 (5.5)	14.1	2164	156 (7.2)	18.7	0.74 (0.59, 0.94)
Fasting serum glucose (mmol/L)							
<5.6	499	34 (6.8)	17.6	430	36 (8.4)	21.6	0.83 (0.52, 1.33)
≥5.6 - <7.0	1032	43 (4.2)	10.3	1115	63 (5.7)	14.2	0.73 (0.50, 1.08)
≥7.0 - <8.3	1679	69 (4.1)	10.2	1634	82 (5.0)	12.5	0.80 (0.58, 1.11)
≥8.3 - <14.0	4387	177 (4.0)	10.1	4407	237 (5.4)	13.5	0.75 (0.62, 0.91)
≥14.0	748	37 (4.9)	12.5	698	47 (6.7)	17.4	0.70 (0.46, 1.08)
Baseline insulin use							
Yes	3566	202 (5.7)	14.3	3445	244 (7.1)	18.1	0.79 (0.66, 0.95)
No	5016	168 (3.3)	8.3	5133	236 (4.6)	11.5	0.73 (0.60, 0.88)
Baseline diabetic medication [c]							
Insulin	3566	202 (5.7)	14.3	3445	244 (7.1)	18.1	0.79 (0.66, 0.95)
Metformin	7020	268 (3.8)	9.5	7048	369 (5.2)	13.1	0.72 (0.62, 0.85)
Sulfonylurea	3615	143 (4.0)	9.9	3707	186 (5.0)	12.7	0.79 (0.63, 0.98)
DPP4 inhibitor	1418	36 (2.5)	6.2	1470	62 (4.2)	10.5	0.62 (0.41, 0.93)
GLP-1 agonist	397	11 (2.8)	6.7	353	20 (5.7)	14.0	0.49 (0.24, 1.03)
Other drugs	13	0	0	21	1 (4.8)	14.2	NA
Baseline diabetic medication in addition to insulin [c]							
Metformin	2582	122 (4.7)	11.8	2498	166 (6.6)	16.9	0.70 (0.55, 0.89)
Metformin + Sulfonylurea	600	29 (4.8)	12.1	643	31 (4.8)	12.1	1.03 (0.62, 1.70)
Metformin + DPP4 inhibitor	304	10 (3.3)	8.2	318	16 (5.0)	12.7	0.69 (0.31, 1.53)
Metformin + GLP-1 agonist	153	3 (2.0)	4.7	138	8 (5.8)	14.4	NA
Metformin + other diabetic medication	88	3 (3.4)	9.1	87	6 (6.9)	18.0	NA
Sulfonylurea	726	32 (4.4)	11.0	768	45 (5.9)	14.8	0.77 (0.49, 1.20)
DPP4 inhibitor	342	10 (2.9)	7.3	383	22 (5.7)	14.5	0.53 (0.25, 1.12)
GLP-1 agonist	189	3 (1.6)	3.8	165	10 (6.1)	14.9	NA
Other drugs or combinations	18	0	0	34	3 (8.8)	24.3	NA

Subgroup Categories	Dapa 10 mg (N=8582) N#	Subjects with events n(%)	Event rate	Placebo (N=8578) N#	Subjects with events n(%)	Event rate	Hazard ratio (95% CI)
Baseline diabetic medication without insulin at baseline [c]							
Metformin	4438	146 (3.3)	8.1	4550	203 (4.5)	11.1	0.74 (0.60, 0.91)
Metformin + Sulfonylurea	2531	94 (3.7)	9.3	2582	117 (4.5)	11.4	0.82 (0.62, 1.08)
Metformin + DPP4 inhibitor	984	22 (2.2)	5.4	995	37 (3.7)	9.2	0.61 (0.36, 1.03)
Metformin + GLP-1 agonist	184	8 (4.3)	10.6	167	9 (5.4)	13.3	0.82 (0.32, 2.14)
Metformin + other diabetic medication	188	3 (1.6)	4.1	199	12 (6.0)	15.6	0.25 (0.07, 0.90)
Sulfonylurea	2889	111 (3.8)	9.6	2939	141 (4.8)	12.1	0.79 (0.62, 1.02)
DPP4 inhibitor	1076	26 (2.4)	5.9	1087	40 (3.7)	9.1	0.67 (0.41, 1.10)
GLP-1 agonist	208	8 (3.8)	9.5	188	10 (5.3)	13.2	0.72 (0.29, 1.84)
Other drugs or combinations	13	0	0	21	1 (4.8)	14.2	NA
Baseline CV medication [c]							
Acetylsalicylic acid	4753	202 (4.2)	10.6	4770	295 (6.2)	15.6	0.68 (0.57, 0.82)
Statin/Ezetimibe	6432	293 (4.6)	11.3	6436	364 (5.7)	14.2	0.80 (0.68, 0.93)
ACE inhibitor/ARB	6974	301 (4.3)	10.8	6970	397 (5.7)	14.3	0.75 (0.65, 0.87)
Dual antiplatelets	793	48 (6.1)	15.3	846	72 (8.5)	21.6	0.70 (0.49, 1.01)
Any antiplatelets	5244	233 (4.4)	11.1	5239	324 (6.2)	15.6	0.71 (0.60, 0.84)
Anticoagulants	529	59 (11.2)	28.6	556	50 (9.0)	23.4	1.23 (0.84, 1.79)
Beta blockers	4498	237 (5.3)	13.2	4527	298 (6.6)	16.6	0.79 (0.67, 0.94)
Calcium channel blockers	2976	151 (5.1)	12.7	3013	199 (6.6)	16.6	0.76 (0.62, 0.94)
Diuretics - loops	866	94 (10.9)	27.9	936	126 (13.5)	36.0	0.76 (0.58, 0.99)
Diuretics - thiazides	1916	86 (4.5)	11.2	1857	97 (5.2)	12.9	0.86 (0.64, 1.15)
Mineralocorticoid receptor antagonist	366	35 (9.6)	24.5	395	47 (11.9)	31.6	0.76 (0.49, 1.18)
Baseline haematuria status							
Positive	1230	77 (6.3)	16.1	1222	87 (7.1)	18.4	0.87 (0.64, 1.19)
Negative	7160	284 (4.0)	9.9	7167	378 (5.3)	13.2	0.75 (0.64, 0.87)
Region							
North America	2737	109 (4.0)	9.7	2731	137 (5.0)	12.4	0.79 (0.61, 1.01)
Latin America	946	40 (4.2)	11.2	931	60 (6.4)	17.5	0.64 (0.43, 0.95)
Asia/Pacific	1093	28 (2.6)	6.6	1093	44 (4.0)	10.5	0.63 (0.39, 1.01)
Europe	3806	193 (5.1)	12.6	3823	239 (6.3)	15.6	0.80 (0.66, 0.97)
Country							
Canada	799	15 (1.9)	4.5	784	27 (3.4)	8.2	0.55 (0.29, 1.03)
United States	1938	94 (4.9)	11.9	1947	110 (5.6)	14.1	0.85 (0.64, 1.11)

Source: Applicant, Clinical Trial Report, Table 11.2.2.1.2.

12.10. Additional Safety Analyses

Table 60 Incidence of Renal Events Assessed by FMQ, Safety Population, DAPA-CKD, On Treatment

	Dapa 10mg (N=2149)		Placebo (N=2149)	
	AE	SAE	AE	SAE
Acute kidney injury (FMQ, narrow)	80 (3.7%)	39 (1.8%)	90 (4.2%)	52 (2.4%)
Acute kidney injury (FMQ, broad)	209 (9.7%)	57 (2.7%)	250 (11.6%)	75 (3.5%)

Table 61 Renal Adverse Events Assessed by FMQ by Baseline eGFR, Safety Population, DAPA-CKD, On Treatment

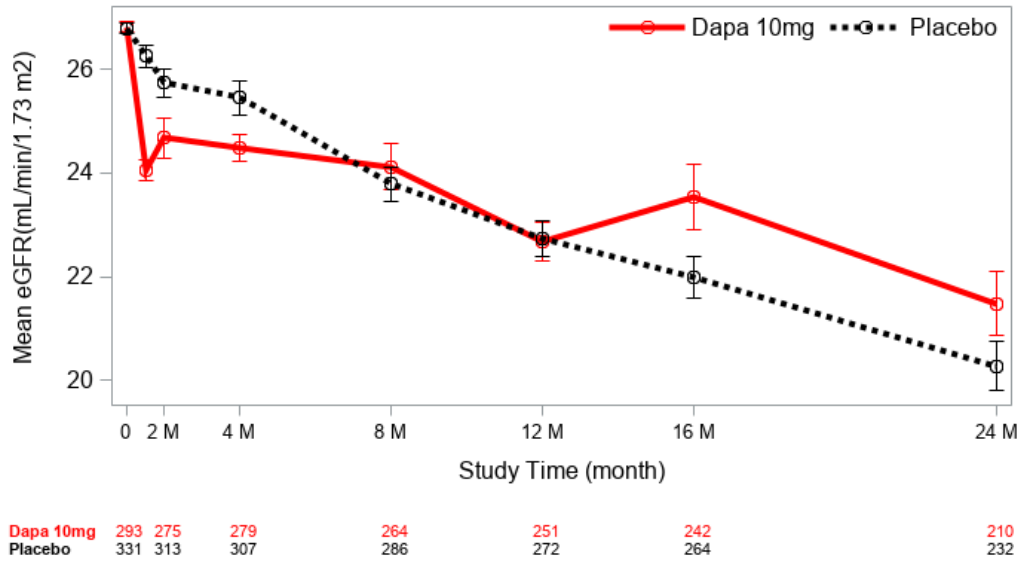
	Dapa 10mg				Placebo			
	<30 (N=293)	30-<45 (N=977)	45-<60 (N=645)	≥ 60 (N=234)	<30 (N=331)	30-<45 (N=917)	45-<60 (N=681)	≥ 60 (N=220)
Acute kidney injury (FMQ narrow)	18 (6.1)	37 (3.8)	18 (2.8)	7 (3.0)	18 (5.4)	41 (4.5)	26 (3.8)	5 (2.3)
ACUTE KIDNEY INJURY	16 (5.5)	35 (3.6)	18 (2.8)	5 (2.1)	18 (5.4)	35 (3.8)	25 (3.7)	3 (1.4)
NEPHROPATHY TOXIC	2 (0.7)	0	0	1 (0.4)	0	3 (0.3)	0	1 (0.5)
CARDIORENAL SYNDROME	0	0	0	0	0	1 (0.1)	0	0
PRERENAL FAILURE	0	0	0	1 (0.4)	0	2 (0.2)	1 (0.1)	0
TUBULOINTERSTITIAL NEPHRITIS	0	1 (0.1)	0	0	0	0	0	0
URATE NEPHROPATHY	0	0	0	0	0	0	0	1 (0.5)
URINE OUTPUT DECREASED	0	1 (0.1)	0	0	0	0	0	0
Acute kidney injury (FMQ broad)	51 (17.4)	101 (10.3)	42 (6.5)	15 (6.4)	62 (18.7)	105 (11.5)	59 (8.7)	24 (10.9)
RENAL IMPAIRMENT	22 (7.5)	22 (2.3)	9 (1.4)	5 (2.1)	18 (5.4)	27 (2.9)	16 (2.3)	10 (4.5)
ACUTE KIDNEY INJURY	16 (5.5)	35 (3.6)	18 (2.8)	5 (2.1)	18 (5.4)	35 (3.8)	25 (3.7)	3 (1.4)
GLOMERULAR FILTRATION RATE DECREASED	8 (2.7)	23 (2.4)	6 (0.9)	1 (0.4)	20 (6.0)	27 (2.9)	12 (1.8)	5 (2.3)
RENAL FAILURE	4 (1.4)	4 (0.4)	2 (0.3)	1 (0.4)	4 (1.2)	6 (0.7)	4 (0.6)	0
BLOOD CREATININE INCREASED	2 (0.7)	15 (1.5)	9 (1.4)	1 (0.4)	7 (2.1)	9 (1.0)	5 (0.7)	7 (3.2)
NEPHROPATHY TOXIC	2 (0.7)	0	0	1 (0.4)	0	3 (0.3)	0	1 (0.5)
BLOOD UREA INCREASED	1 (0.3)	4 (0.4)	1 (0.2)	0	0	1 (0.1)	1 (0.1)	0
AZOTAEMIA	0	0	0	0	0	0	1 (0.1)	0
CARDIORENAL SYNDROME	0	0	0	0	0	1 (0.1)	0	0
CREATININE RENAL CLEARANCE DECREASED	0	0	0	0	1 (0.3)	1 (0.1)	0	0
HYPERCREATINAEMIA	0	1 (0.1)	0	0	0	0	0	0
PRERENAL FAILURE	0	0	0	1 (0.4)	0	2 (0.2)	1 (0.1)	0
TUBULOINTERSTITIAL NEPHRITIS	0	1 (0.1)	0	0	0	0	0	0
URATE NEPHROPATHY	0	0	0	0	0	0	0	1 (0.5)
URINE OUTPUT DECREASED	0	1 (0.1)	0	0	0	0	0	0

Table 62 Renal Adverse Events Assessed by FMQ Acute Renal Injury (broad) by Baseline eGFR across Study Time Points, Safety Population, DAPA-CKD, On Treatment

	Dapa 10mg				Placebo			
	<30 (N=293)	30-<45 (N=977)	45-<60 (N=645)	≥ 60 (N=234)	<30 (N=331)	30-<45 (N=917)	45-<60 (N=681)	≥ 60 (N=220)
Acute renal injury AEs (FMQ broad)	51 (17.4)	101 (10.3)	42 (6.5)	15 (6.4)	62 (18.7)	105 (11.5)	59 (8.7)	24 (10.9)
≤0.5 M	3 (1.0)	8 (0.8)	3 (0.5)	0	2 (0.6)	2 (0.2)	3 (0.4)	2 (0.9)
>0.5-2 M	6 (2.0)	10 (1.0)	4 (0.6)	0	6 (1.8)	9 (1.0)	2 (0.3)	5 (2.3)
>2-4 M	8 (2.7)	15 (1.5)	9 (1.4)	1 (0.4)	6 (1.8)	9 (1.0)	7 (1.0)	2 (0.9)
>4-8 M	10 (3.4)	9 (0.9)	4 (0.6)	0	9 (2.7)	14 (1.5)	7 (1.0)	1 (0.5)
>8-12 M	4 (1.4)	14 (1.4)	6 (0.9)	4 (1.7)	11 (3.3)	18 (2.0)	11 (1.6)	3 (1.4)
>12-16 M	6 (2.0)	13 (1.3)	5 (0.8)	2 (0.9)	9 (2.7)	15 (1.6)	6 (0.9)	3 (1.4)
>16-20 M	7 (2.4)	11 (1.1)	3 (0.5)	1 (0.4)	7 (2.1)	14 (1.5)	4 (0.6)	2 (0.9)
>20-24 M	2 (0.7)	6 (0.6)	6 (0.9)	3 (1.3)	4 (1.2)	13 (1.4)	7 (1.0)	2 (0.9)
>24-28 M	5 (1.7)	8 (0.8)	1 (0.2)	1 (0.4)	8 (2.4)	5 (0.5)	8 (1.2)	3 (1.4)
>28-32 M	0	4 (0.4)	1 (0.2)	3 (1.3)	0	6 (0.7)	4 (0.6)	1 (0.5)
>32 M	0	3 (0.3)	0	0	0	0	0	0
Acute renal injury SAEs (FMQ broad)								
Acute kidney injury	14 (4.8)	21 (2.1)	8 (1.2)	3 (1.3)	15 (4.5)	37 (4.0)	13 (1.9)	2 (0.9)
>0.5-2 M	2 (0.7)	1 (0.1)	1 (0.2)	0	3 (0.9)	0	1 (0.1)	1 (0.5)
>2-4 M	1 (0.3)	4 (0.4)	3 (0.5)	1 (0.4)	1 (0.3)	2 (0.2)	4 (0.6)	0
>4-8 M	2 (0.7)	1 (0.1)	1 (0.2)	0	2 (0.6)	5 (0.5)	1 (0.1)	0
>8-12 M	3 (1.0)	2 (0.2)	1 (0.2)	2 (0.9)	3 (0.9)	8 (0.9)	2 (0.3)	0
>12-16 M	2 (0.7)	2 (0.2)	1 (0.2)	0	2 (0.6)	4 (0.4)	1 (0.1)	1 (0.5)
>16-20 M	1 (0.3)	2 (0.2)	0	0	1 (0.3)	5 (0.5)	0	0
>20-24 M	1 (0.3)	0	0	0	2 (0.6)	7 (0.8)	2 (0.3)	0
>24-28 M	2 (0.7)	7 (0.7)	1 (0.2)	0	1 (0.3)	2 (0.2)	1 (0.1)	0
>28-32 M	0	2 (0.2)	0	0	0	4 (0.4)	1 (0.1)	0

Source: Reviewer's table, dataset: adsl & adae, OCS Analysis Studio-Custom Table Tool
Abbreviation: M, month

Figure 37 Mean eGFR over Time in Subjects with Baseline eGFR < 30 mL/min/1.73m^2



Source: Reviewer's analysis, dataset: adsl & adlb

Figure 38 Mean eGFR over Time in Subjects with Baseline eGFR 30-<45 mL/min/1.73m^2

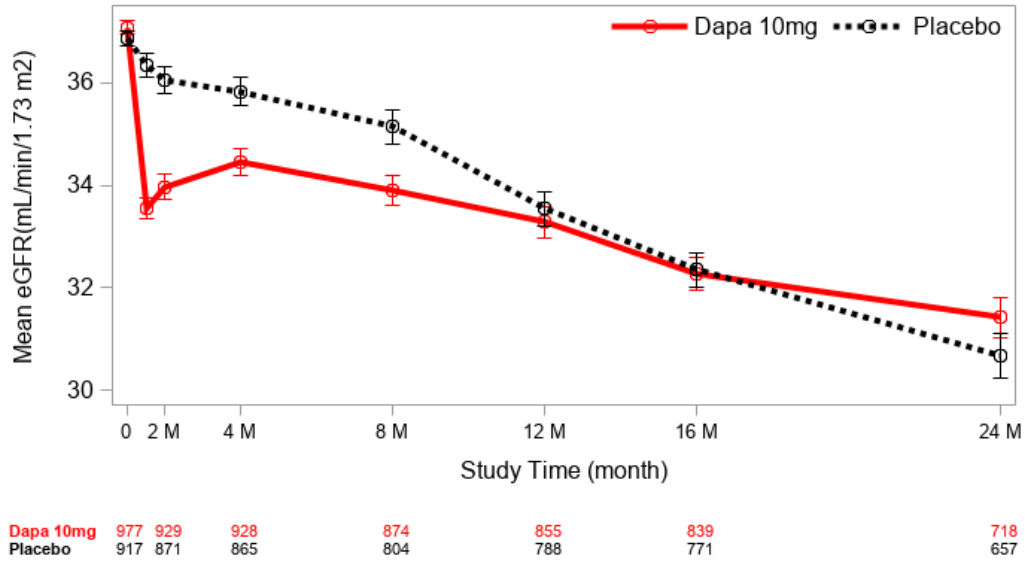
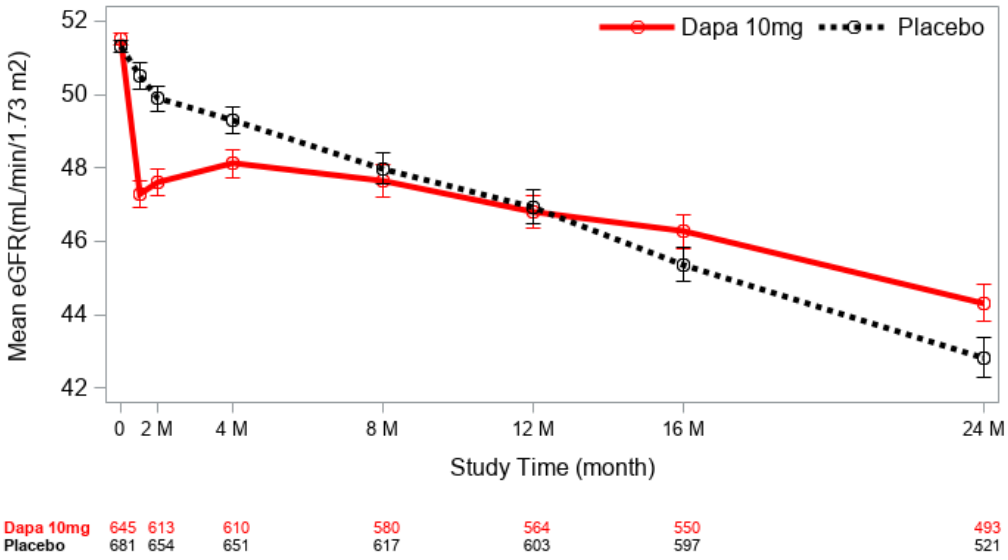
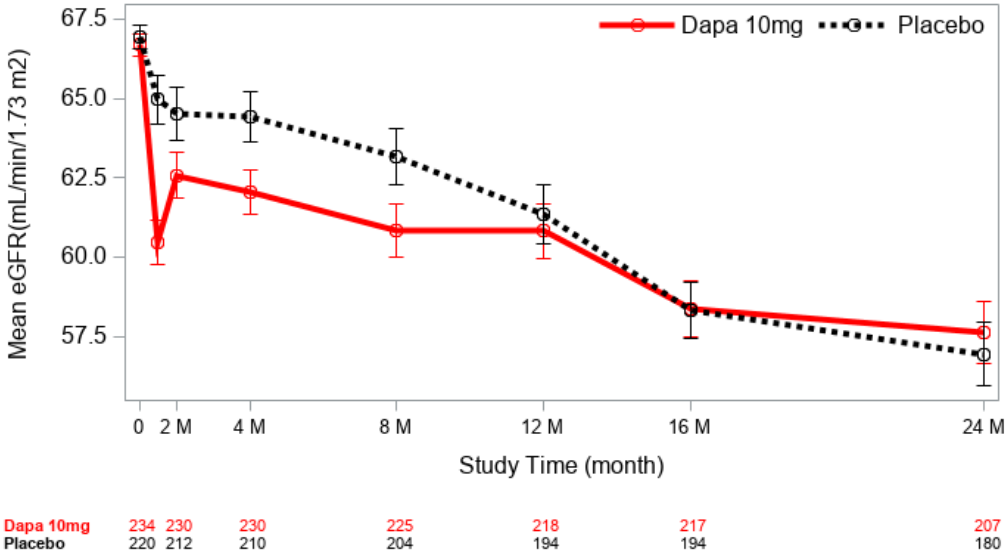


Figure 39 Mean eGFR over Time in Subjects with Baseline eGFR 45-<60 mL/min/1.73m^2



Dapa 10mg	645	613	610	580	564	550	493
Placebo	681	654	651	617	603	597	521

Figure 40 Mean eGFR over Time in Subjects with Baseline eGFR ≥ 60 mL/min/1.73m^2



Dapa 10mg	234	230	230	225	218	217	207
Placebo	220	212	210	204	194	194	180

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sabry Soukehal, RAC
Pharmacometrics Team Leader	Justin Earp, PhD
Deputy Division Director (OCP/DP)	Hao Zhu, PhD
Clinical Reviewers	Efficacy reviewer: Tania Condarco, MD Safety reviewer: Tzu-Yun McDowell, PhD Pediatrics reviewer: Kirtida Mistry, MBBCh, DCH, MRCPCH
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Statistical Reviewer	William Koh, PhD
Statistical Team Leader	Jialu Zhang, PhD
Cross-Disciplinary Team Leader	Kimberly Smith, MD, MS
Division Director (OB)	Mark Rothmann, PhD
Deputy Division Director (Clinical)	Aliza Thompson, MD, MS

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Division Director (OB)	Mark Rothman, PhD	OB/DBII	Sections: 7.1.1, 7.1.2, 7.1.6	**Select one:** ___ Authored __√_ Approved
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